Prognostic Influence of Diabetes Mellitus on Long-Term Clinical Outcomes and Stent Thrombosis After Drug-Eluting Stent Implantation in Asian Patients

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Diabetes mellitus has been associated with an increased risk of mortality and stent thrombosis after implantation of drug-eluting stents (DES). Little is known about the prognostic impact of diabetes on clinical outcomes in an Asian population treated with DES. We compared adverse outcomes between 865 patients with diabetes and 2,295 patients without diabetes treated with DES after adjustment for differences in baseline risk factors in the patients. The primary outcome was the composite of death, nonfatal myocardial infarction, or target-vessel revascularization (TVR). The 3-year unadjusted rates of death (5.8% vs 3.5%, p = 0.002) and TVR (12.2% vs 8.6%, p = 0.003) were significantly higher in patients with diabetes. After adjustment for baseline differences, the risk of TVR remained higher in patients with diabetes (hazard ratio 1.37, 95% confidence interval [CI] 1.04 to 1.81, p = 0.03), but the risk of death did not (hazard ratio 1.35, 95% CI 0.89 to 2.05, p = 0.16). The 3-year adjusted risk of the primary composite outcome was significantly higher in patients with diabetes compared with patients without diabetes (23.3% vs 16.1%, hazard ratio 1.24, 95% CI 1.02 to 1.51, p = 0.03). Insulin use was an independent predictor for each outcome (death, TVR, and composite outcome). After adjustment by baseline risk profile and for propensity, diabetes was not associated with an increased risk of stent thrombosis (multivariable-adjusted hazard ratio 0.87, 95% CI 0.36 to 2.15, p = 0.77 and propensity-adjusted hazard ratio 0.87, 95% CI 0.37 to 2.06, p = 0.76). In conclusion, diabetic status was associated with increased TVR without a significantly increased rate of death. A diabetes-associated excess risk of stent thrombosis was not observed in Asian patients. © 2009 Elsevier Inc. **(Am J Cardiol 2009;103:646–652)**

Drug-eluting stents (DES) have markedly reduced the incidence of restenosis as compared with bare-metal stents (BMS) both in patients with diabetes and patients without diabetes.[1,2] However, the long-term safety of DES has been questioned by several studies, which have reported increased rates of death, myocardial infarction (MI), and late stent thrombosis (ST) compared with BMS.[3,4] In particular, a recent report suggests that the long-term survival rate is lower in patients with diabetes treated with DES than in those treated with BMS.[5] Diabetes has also been an independent predictor of ST in patients treated with DES.[6,7] Direct extrapolation of the available evidence into clinical practice for the Asian population may not be warranted because the impact of diabetes and its clinical consequence in patients who receive DES may differ according to ethnicity. In contrast to findings in Western populations, previous studies have suggested that the prognostic relevance of diabetes on clinical outcomes and ST is less apparent in Asian patients.[8,9] In addition, ethnic differences in the risk of cardiovascular events were suggested in a large international study.[10] We therefore determined whether diabetes mellitus was associated with an increased risk of long-term clinical events and ST in a large group of Asian patients with the unrestricted use of DES.

Methods

The study population consisted of consecutive patients who underwent DES implantation at 2 academic hospitals (Asan Medical Center, Seoul, and Asan Medical Center, GangNeung) in Korea between February 19, 2003, and February 28, 2006. Since February 2003, DES has been used as a default strategy for percutaneous coronary intervention except in patients with anticipated major surgery necessitating antiplatelet therapy, lesions in a large vessel without an available DES size, and a patient's refusal.[11]

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Table 1
Baseline characteristics of the overall patient population

Variable	Diabetes Mellitus		p Value
	Yes (n = 865)	No (n = 2,295)	
Age (yrs)	62.7 ± 9.1	59.7 ± 10.6	<0.001
Women	312 (36.1)	619 (27.0)	<0.001
Hypertension	533 (61.6)	1,066 (46.4)	<0.001
Lipid profiles			
Total cholesterol (mg/dl)	178.2 ± 53.3	172.2 ± 48.5	0.003
Triglyceride (mg/dl)	161.2 ± 102.8	147.0 ± 93.5	0.005
HDL cholesterol (mg/dl)	41.9 ± 17.3	43.2 ± 15.1	0.10
LDL cholesterol (mg/dl)	100.5 ± 58.4	104.7 ± 38.0	0.06
Current smoker	201 (23.2)	719 (31.3)	<0.001
Renal failure (creatinine >2.0 mg/dl)	50 (5.8)	30 (1.3)	<0.001
Previous MI	99 (11.4)	198 (8.6)	0.02
Previous coronary angioplasty	161 (18.6)	383 (16.7)	0.20
Previous coronary artery bypass graft	31 (3.6)	53 (2.3)	0.05
Clinical indication for index procedure			<0.001
Stable angina pectoris	450 (52.0)	1,074 (46.8)	
Unstable angina pectoris	334 (38.6)	865 (37.7)	
Myocardial infarction	81 (9.4)	356 (15.5)	
Multivessel coronary disease	585 (67.6)	1,280 (55.8)	<0.001
Left ventricular ejection fraction (%)	57.9 ± 9.3	58.6 ± 8.7	0.04
Medications at discharge			
Warfarin	10 (1.2)	21 (0.9)	0.54
Statin	498 (57.6)	1,240 (54.0)	0.07
β blocker	631 (72.9)	1,629 (71.0)	0.28
Calcium channel blocker	417 (48.2)	1,129 (49.2)	0.62
ACE inhibitor	536 (62.0)	1,271 (55.4)	0.001
Treated lesions	1,301	3,190	
Left anterior descending	637 (49.0)	1,579 (49.5)	0.74
Left main	83 (6.4)	224 (7.0)	0.44
Lesion characteristics			
ACC/AHA type B2 or C lesion	1,008 (77.5)	2,330 (73.0)	0.002
Ostial	84 (6.5)	271 (8.5)	0.02
Bifurcation	236 (18.1)	501 (15.7)	0.05
Total occlusion	70 (5.4)	181 (5.7)	0.70
Restenotic lesion	68 (5.2)	183 (5.7)	0.50
Procedural characteristics			
Direct stenting	174 (13.4)	553 (17.3)	0.001
Intravascular ultrasound guidance	798 (61.3)	2,099 (65.8)	0.01
DES type			0.06
Sirolimus-eluting stent	976 (75.0)	2,478 (77.7)	
Paclitaxel-eluting stent	325 (25.0)	712 (22.3)	
Number of stents per patient	2.1 ± 1.2	1.8 ± 1.1	<0.001
Total stent length per patient (mm)	53.5 ± 33.3	46.0 ± 29.8	<0.001
Average stent diameter per patient (mm)	3.1 ± 0.3	3.2 ± 0.3	<0.001
Use of glycoprotein IIb/IIIa inhibitors	24 (2.8)	69 (3.0)	0.73
Duration of clopidogrel use (months)	12.6 ± 8.6	11.5 ± 7.7	0.001

Data are mean ± SD or number (%).

ACE = angiotensin-converting enzyme; ACC/AHA = American College of Cardiology/American Heart Association classification; DES = drug-eluting stents; HDL = high-density lipoprotein; LDL = low-density lipoprotein; MI = myocardial infarction.

Patients who underwent coronary brachytherapy were excluded from the study population.

Stent implantation methods have been described previously.[12] The choice of the specific type of DES—sirolimus-eluting (Cypher, Cordis, Johnson and Johnson, Miami Lakes, Florida) or paclitaxel-eluting (Taxus, Boston Scientific, Natick, Massachusetts)—was left to the operator's discretion. Patients were prescribed aspirin plusclopidogrel 75 mg/day after a loading dose of 300 or 600 mg before or during the coronary intervention. After the procedure, patients were prescribed aspirin indefinitely and clopidogrel for ≥6 months regardless of stent type.[8] The use of glycoprotein IIb/IIIa inhibitors was also left to the physician's discretion. This study was approved by the local institutional review board, and written informed consent was obtained from all patients for the use of clinical and percutaneous coronary intervention data.

Table 2
Crude and adjusted hazard ratios of clinical outcomes according to diabetic status

Outcome	Outcome Rates (%) at 3 Years*		Crude		Multivariable Adjusted†		Adjusted for Propensity		Adjusted for Propensity and All Covariates	
	DM	Non-DM	Hazard Ratio (95% CI)	p Value	Hazard Ratio (95% CI)	p Value	Hazard Ratio (95% CI)	p Value	Hazard Ratio (95% CI)	p Value
Death	5.8	3.5	1.82 (1.25–2.64)	0.002	1.35 (0.89–2.05)	0.16	1.37 (0.91–2.06)	0.13	1.35 (0.89–2.04)	0.16
MI	7.6	5.4	1.45 (1.08–1.96)	0.02	1.08 (0.78–1.50)	0.63	1.07 (0.77–1.48)	0.68	1.07 (0.77–1.49)	0.68
TLR	9.6	8.4	1.14 (0.86–1.51)	0.38	1.06 (0.78–1.43)	0.71	1.04 (0.77–1.40)	0.82	1.05 (0.78–1.42)	0.75
TVR	12.2	8.6	1.48 (1.14–1.91)	0.003	1.37 (1.04–1.81)	0.03	1.33 (1.01–1.76)	0.04	1.36 (1.03–1.80)	0.03
Death or MI	13.5	8.9	1.6 (1.27–2.02)	0.001	1.18 (0.92–1.53)	0.20	1.17 (0.91–1.51)	0.22	1.17 (0.91–1.52)	0.22
Death, MI, or TVR	23.3	16.1	1.55 (1.29–1.85)	<0.001	1.24 (1.02–1.51)	0.03	1.24 (1.02–1.51)	0.03	1.24 (1.02–1.50)	0.04

CI = confidence interval; DM = diabetes mellitus; MI = myocardial infarction; TLR = target-lesion revascularization; TVR = target-vessel revascularization.

* Event rates were calculated with the use of Kaplan-Meier methods.

† Adjustments were made for baseline variables listed in Table 1.

The diabetic subgroup was defined as all patients receiving active treatment with oral hypoglycemic agents or insulin. Patients with diet-controlled diabetes were included only if there was documentation of an abnormal blood glucose level after an overnight fast or an abnormal glucose-tolerance test available during the hospitalization for percutaneous coronary intervention.

The primary end point of the study was the composite outcome of death, nonfatal MI, or target-vessel revascularization (TVR) at 3 years. Secondary end points were death, MI, revascularization of the target lesion or target vessel, ST, and the composite of death or MI. MI was defined as the presence of new Q waves on the electrocardiogram or an elevation of creatine kinase-MB isoenzyme to ≥3 times the upper limit of normal range in ≥2 blood samples. Target-lesion revascularization was defined as revascularization for a stenosis within the stent or within the 5-mm borders adjacent to the stent. TVR was defined as repeat percutaneous coronary intervention or bypass grafting of the target vessel. The occurrence of ST was assessed by the Academic Research Consortium definitions.[13] All clinical outcomes of interest were adjudicated by the local events committee at the University of Ulsan College of Medicine, Asan Medical Center, Seoul.

Clinical, procedural, and outcome data were recorded in dedicated databases by independent research personnel.[14] Clinical follow-up was performed via office visit or telephone contact at 1, 6, and 12 months after the procedure and every 6 months thereafter. To ensure accurate assessment of clinical end points, additional information was obtained from visits or telephone contacts with living patients or family members and from medical records obtained from other hospitals, as necessary.

For validation of complete follow-up data, information about vital status was obtained from the National Population Registry of the Ministry of Government Administration and Home Affairs using a unique personal identification number. Data regarding rehospitalization for follow-up MI were obtained from the Hospital Disease Code Registration System categorized according to the International Classification of Disease, tenth revision, which was merged for reimbursement in the Health Insurance Review Agency in Korea.

Continuous variables were compared with the *t* test or Wilcoxon's rank sum test, and categorical variables were compared with the chi-square statistics or Fisher's exact test, as appropriate. Survival curves were constructed using Kaplan-Meier estimates and compared with the log-rank test. Patients who did not experience an outcome of interest were censored at the last known date of contact.

Cox proportional hazards regression was used to determine whether the long-term event-free survival rate differed significantly between patients with diabetes and patients without diabetes after controlling for differences in preprocedural risks. Adjusted covariates included the patient's demographics, the presence or absence of a variety of medical conditions or coexisting risk factors, cardiac presentation, disease extent, measures of ventricular function, medical regimen on discharge, and angiographic and procedural characteristics as listed in Table 1. The proportional hazards assumption was confirmed through examination of log (-log [survival]) curves and testing of partial (Schoenfeld) residuals,[15] and no relevant violations were found.

In addition, propensity score analysis was performed to determine the causal effect of diabetes on outcomes.[16] Propensity score analysis has also been proposed as more practical than a standard regression analysis when the number of events is low, such as ST, relative to the number of confounders.[17,18] Briefly, propensity scores were estimated using multiple logistic regression without regard to outcome variables. A full nonparsimonious model was developed that included all variables listed in Table 1. This model yielded a c-statistic of 0.91, and a Hosmer-Lemeshow goodness-of-fit test p value of 0.35, indicating excellent discrimination. The individual propensity score was incorporated into Cox proportional hazard regression models as a covariate as well as diabetic status to calculate the propensity-adjusted hazard ratios.

Independent predictors of outcomes of interest were identified using a multivariable Cox regression model with a backwards elimination technique (retention threshold $p < 0.05$). All statistical analyses were performed using SAS version 9.1 (SAS Institute, Cary, North Carolina). A 2-tailed p value of <0.05 was considered statistically significant.

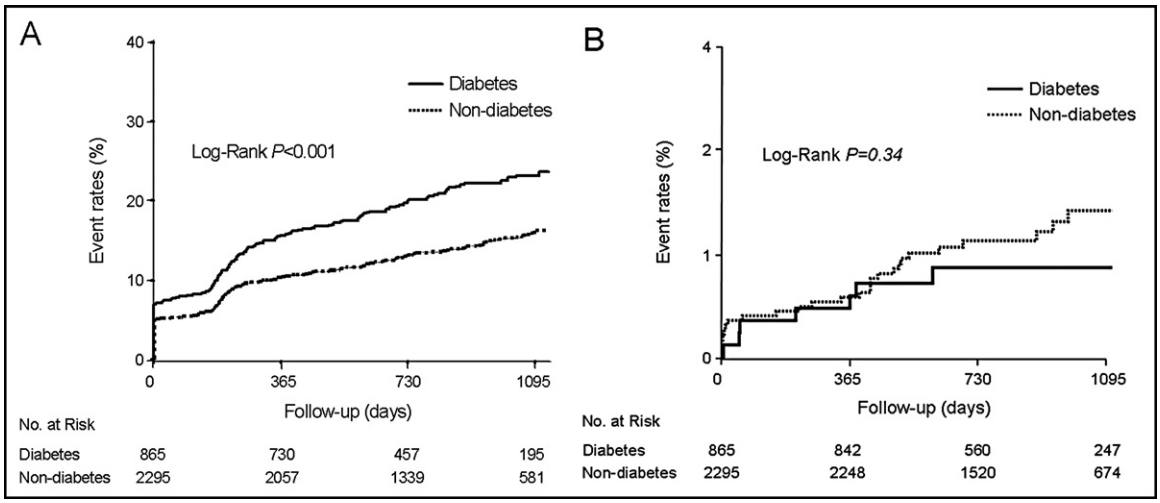

Figure 1. Kaplan-Meier survival curve of primary composite end point *(A)* and stent thrombosis (definite or probable) *(B)*.

Table 3
Crude and adjusted hazard ratios of stent thrombosis according to diabetic status

Outcome (ARC criteria)	Outcome Rates (%) at 3 Years*		Crude		Multivariable Adjusted†		Adjusted for Propensity		Adjusted for Propensity and All Covariates	
	DM	Non-DM	Hazard Ratio (95% CI)	p Value	Hazard Ratio (95% CI)	p Value	Hazard Ratio (95% CI)	p Value	Hazard Ratio (95% CI)	p Value
Definite	0.5	1.2	0.45 (0.16–1.29)	0.14	0.62 (0.20–1.94)	0.41	0.62 (0.21–1.84)	0.39	0.64 (0.21–1.99)	0.44
Definite or probable	0.9	1.4	0.67 (0.29–1.54)	0.35	0.87 (0.36–2.15)	0.77	0.87 (0.37–2.06)	0.76	0.90 (0.37–2.21)	0.82
Any	3.1	2.3	1.34 (0.81–2.22)	0.25	1.14 (0.66–2.00)	0.64	1.18 (0.69–1.99)	0.55	1.14 (0.66–1.99)	0.64

ARC = Academic Research Consortium; CI = confidence interval; DM = diabetes mellitus.
* Event rates were calculated with the use of Kaplan-Meier methods.
† Adjustments were made for baseline variables listed in Table 1.

Results

Between February 2003 and February 2006, 3,160 patients underwent DES implantation. The median duration of follow-up was 29.5 months (interquartile range 21.4 to 37.5 months). Diabetes mellitus was present in 865 patients, accounting for 27.4% of the overall population. Of the patients with diabetes, 148 (17.1%) were being treated with insulin, 663 (76.6%) were being treated with oral hypoglycemic agents, and 54 (6.2%) were diet-controlled.

Baseline characteristics according to diabetic status are summarized in Table 1. Patients with diabetes were on average older and were more likely to be women, to have other coexisting conditions (hypertension, a higher level of serum cholesterol and triglyceride, renal failure, previous MI, and multivessel disease), to present more often with stable angina, and to have lower ejection fractions. Patients with diabetes also had higher risk angiographic (e.g., American College of Cardiology/American Heart Association [ACC/AHA] type B2 or C bifurcation) and procedural (e.g., higher number of implanted stents, longer stent length, and smaller stent diameter) characteristics. Duration of clopidogrel use was longer in patients with diabetes.

Table 2 summarizes clinical outcomes based on diabetic status. In a crude analysis, the rate of death (5.8% vs 3.5%, p = 0.002), nonfatal MI (7.6% vs 5.4%, p = 0.02), and the composite outcome of death or MI (13.5% vs 8.9%, p = 0.02) at 3 years was significantly higher in patients with diabetes than in patients without diabetes. However, after multivariable-adjusted Cox regression analysis, the risks of death, MI, and their composite were similar in the 2 groups. The same held true after propensity adjustment. The rate of target-lesion revascularization during the 3-year follow-up period was similar in the diabetic and nondiabetic groups (9.6% vs 8.4%, p = 0.38). However, in a crude analysis and after adjusting for other confounders or propensity, the risk of TVR was significantly higher in patients with diabetes than in patients without diabetes. Finally, the primary composite outcome of death, MI, or TVR was significantly higher in patients with diabetes than in patients without diabetes, primarily due to an increased need for TVR (Table 2 and Figure 1).

Table 3 summarizes the rate of ST ≤3 years in the diabetic and nondiabetic groups. Of 23 patients who had ST in the diabetic group, 11 (48%) were on dual antiplatelet therapy, 9 (39%) were on aspirin monotherapy, and 3 (13%) were not on antiplatelet therapy at the time of ST. In 46 patients who had ST in the nondiabetic group, 21 (46%) were on dual antiplatelet therapy, 20 (44%) were on aspirin monotherapy, and 5 (11%) were not on antiplatelet therapy (p for trend = 1.0). The observed (unadjusted) risk of ST by

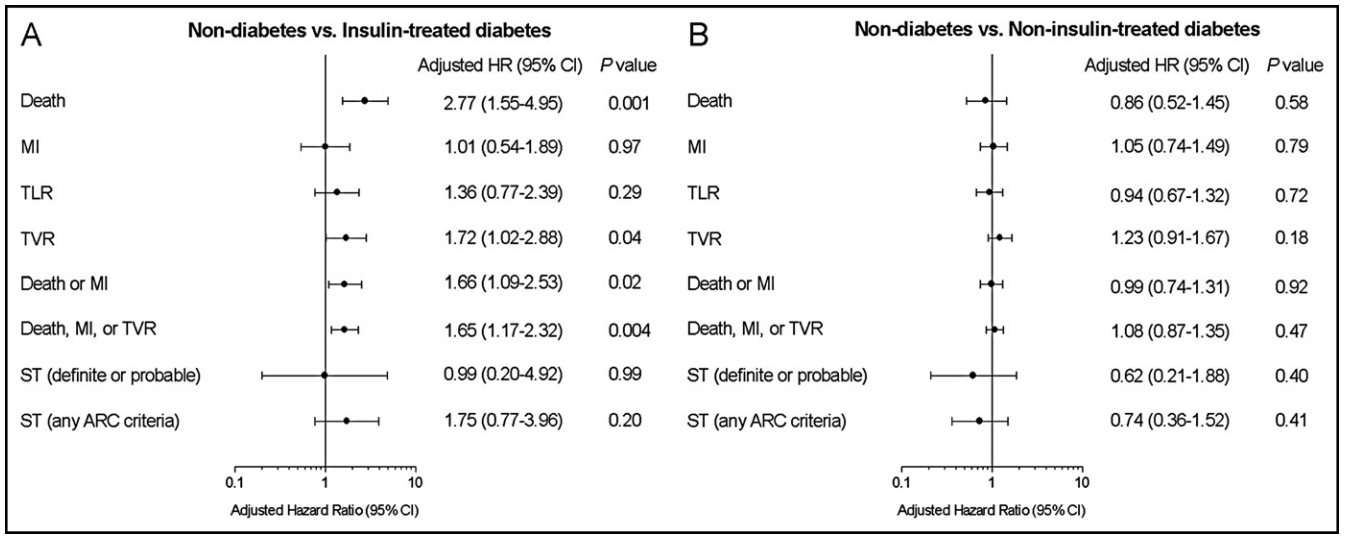

Figure 2. Adjusted hazard ratios for clinical outcomes and stent thrombosis in diabetic patients who do (A) and do not (B) require insulin therapy versus non-diabetic patients. ARC = Academic Research Consortium; MI = myocardial infarction; ST = stent thrombosis; TLR = target-lesion revascularization; TVR = target-vessel revascularization.

Table 4
Independent predictors of clinical events

Predictors	Hazard Ratio (95% CI)	p Value
Death		
Insulin-treated diabetes	3.70 (2.21–6.21)	<0.001
Renal failure	2.63 (1.40–4.95)	0.003
Women	1.70 (1.09–2.65)	0.02
Age (per 1-year increase)	1.06 (1.04–1.08)	<0.001
Left ventricular ejection fraction (per 1%-increase)	0.97 (0.96–0.99)	0.003
Target-vessel revascularization		
Insulin-treated diabetes	1.75 (1.10–2.78)	0.02
Previous coronary angioplasty	1.64 (1.22–2.19)	0.001
Paclitaxel-eluting stent	1.59 (1.19–2.11)	0.002
ACC/AHA type B2 or C lesion	1.49 (1.02–2.19)	0.04
Number of stents (per 1-number increase)	1.23 (1.16–1.36)	<0.001
Age (per 1-year increase)	0.98 (0.96–0.99)	<0.001
Average stent diameter (per 1-mm increase)	0.57 (0.37–0.89)	0.01
Composite end point (death, MI, or TVR)		
Renal failure	2.14 (1.42–3.22)	<0.001
Insulin-treated diabetes	1.82 (1.33–2.50)	<0.001
Paclitaxel-eluting stent	1.40 (1.14–1.72)	0.001
ACC/AHA type B2 or C lesion	1.32 (1.01–1.74)	0.04
Previous coronary angioplasty	1.31 (1.05–1.63)	0.02
Multivessel disease	1.29 (1.05–1.58)	0.02
Total stent length (per 1-mm increase)	1.007 (1.004–1.010)	<0.001
Average stent diameter (per 1-mm increase)	0.72 (0.52–0.98)	0.04

ACC/AHA = American College of Cardiology/American Heart Association; CI = confidence interval; MI = myocardial infarction; TVR = target-vessel revascularization.

Table 5
Independent predictors of stent thrombosis

Predictors	Hazard Ratio (95% CI)	p Value
Definite		
Premature cessation of antiplatelet therapy	16.81 (5.26–53.79)	<0.001
Acute MI	5.32 (2.35–12.09)	<0.001
Restenotic lesion	3.99 (1.27–12.50)	0.02
Paclitaxel-eluting stent	2.26 (1.00–5.12)	0.05
Age (per 1-year increase)	0.95 (0.91–0.98)	0.001
Definite or probable		
Premature cessation of antiplatelet therapy	9.04 (3.04–26.88)	<0.001
Acute MI	6.64 (3.19–13.83)	<0.001
Restenotic lesion	4.55 (1.64–12.65)	0.004
Paclitaxel-eluting stent	2.22 (1.06–4.62)	0.03
Total stent length (per 1-mm increase)	1.01 (1.003–1.02)	0.01
Age (per 1-year increase)	0.96 (0.93–0.99)	0.01
Any ARC criteria		
Premature cessation of antiplatelet therapy	7.12 (3.58–14.15)	<0.001
Renal failure	5.76 (2.79–11.92)	<0.001
Acute MI	2.54 (1.47–4.38)	0.001
Total stent length (per 1-mm increase)	1.01 (1.003–1.02)	0.004
Left ventricular ejection fraction (per 1%-increase)	0.96 (0.94–0.98)	0.001

ARC = Academic Research Consortium; CI = confidence interval; MI = myocardial infarction.

the Academic Research Consortium definitions did not differ significantly between the 2 groups (Table 3 and Figure 1). After adjustment for covariates or propensity score, there was no association between diabetes and the risk of ST. The adjusted risk of early (hazard ratio 0.56, 95% CI 0.07 to 4.74, p = 0.59), late (hazard ratio 1.06, 95% CI 0.41 to 2.70, p = 0.91), and very late (hazard ratio 1.40, 95% CI 0.66 to 2.93, p = 0.38) ST was also similar in the 2 groups.

Figure 2 shows a comparison of adjusted hazard ratios of clinical outcomes in patients with diabetes receiving or not receiving insulin treatment versus in patients without dia-

betes. Compared with patients without diabetes, there was an increased risk of death, TVR, and the composite of death or MI in patients with insulin-treated diabetes but not in patients with diabetes not treated with insulin. The adjusted risk of the primary composite outcome (death, MI, or TVR) was significantly higher in insulin-treated diabetes (adjusted hazard ratio 1.65, 95% CI 1.17 to 2.32, p = 0.004), but not in noninsulin-treated diabetes (adjusted hazard ratio 1.08, 95% CI 0.87 to 1.35, p = 0.47), compared with patients without diabetes. However, there was no evidence of a relationship between ST risk and diabetic status regardless of insulin treatment status (Figure 2).

Independent predictors of long-term clinical events and ST are listed in Tables 4 and 5. Insulin-treated diabetes was independently associated with an increased risk of death, TVR, or the primary composite of death, MI, or TVR (Table 4). However, the risk of ST was not associated with diabetic status (Table 5). The independent predictors of ST included premature cessation of antiplatelet therapy, renal failure, acute MI, restenotic lesion, paclitaxel-eluting stent, total stent length, age, and low left ventricular ejection fraction.

Discussion

The major findings of our study of DES use in patients with diabetes are (1) the overall adjusted mortality rate was similar in patients with diabetes and patients without diabetes; (2) patients with diabetes have a higher incidence of TVR without a significantly increased rate of target-lesion revascularization; (3) insulin-treated diabetes was independently associated with increased risk of death and TVR; and (4) there was no significant association between increased risk of ST and diabetes whether insulin-dependent.

For mortality with DES relative to BMS, the impact of diabetes reported in several clinical trials and registries has varied.[5,19,20] The j-Cypher registry, a large DES registry in Japan that includes 5,115 real-world patients treated with DES, showed a similar survival rate compared with those of patients with BMS.[21] In this study, diabetes did not adversely affect long-term mortality. A recent report of 2,557 Western patients treated with DES showed significantly higher 3-year mortality rates in patients with diabetes (35% insulin-dependent) than in patients without diabetes.[22] In contrast, our results showed that patients with and without diabetes had similar adjusted risks of 3-year mortality. However, we found that insulin-treated diabetes was an independent predictor of mortality. The smaller proportion of insulin-requiring diabetes (17% in ours, 23% in j-Cypher registry) compared with Western countries (35%)[22] may explain the discrepancies in the prognostic impact of diabetes on long-term mortality. Although comparative data are not available, differences in ethnicity, clinical indications, medical treatment variations and practice patterns may be also responsible for these discrepancies between Asian and Western populations. The REduction of Atherothrombosis for Continued Health (REACH) registry of 68,236 global populations has shown marked ethnic differences in rates of cardiovascular death.[10]

We previously reported that patients with diabetes treated with DES experience similar rates of angiographic restenosis and target-lesion revascularization compared with those without diabetes.[23] Similar findings have recently been reported by a different group.[22] However, in another study, diabetes mellitus has been independently associated with an increased risk of angiographic restenosis, target-lesion revascularization, or TVR.[24] In our study, the rate of TVR was significantly higher in patients with diabetes without a significant increase of target-lesion revascularization compared with patients without diabetes. These results suggested that a greater need for additional revascularization over longer-term periods in patients with diabetes was mainly due to late progression of coronary artery disease at untreated sites not restenosis, indicating the long-term durability of DES on the stented segment.

Another issue that requires comment is that not only patients with diabetes but also patients with impaired glucose regulation have increased cardiovascular risk associated with plaque instability.[25,26] In the present study, we did not have detailed access to glucose tolerance in groups without diabetes, which would have been of interest. Thus, further studies with comprehensive laboratory assessment are needed to fully understand the prognostic impact of glucose tolerance (e.g., impaired glucose tolerance and impaired fasting glucose) on cardiovascular events.

Several limitations of our analysis deserve comment. Our study evaluated nonrandomized, observational data. Given the low incidence of ST, larger studies with longer-term follow-up are required to detect small difference in event rates. Because direct comparison between ethnic groups was not performed, statement about possible ethnic differences regarding the impact of diabetes on the risk of clinical outcomes and ST may be not confirmative, but should be considered hypothesis-generating. The lack of comparison between DES and BMS did not allow us to mention the relative effectiveness and safety of both types of stent in patients with diabetes. The diagnosis of ST proposed by Academic Research Consortium definitions was based on clinical presentation and coronary angiography. Given the high incidence of silent ischemia in patients with diabetes, the consideration of silent ischemia may further be helpful for interpreting the relation between diabetes and ST. Although propensity analysis can rigorously adjust for cofounders and provide some information about the causal effect, unobserved covariates could not be controlled. Finally, considering the diversities in percutaneous coronary intervention practice in Asian countries, larger international studies may be warranted to generalize the current findings.

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