Impact of Diabetes Among Revascularized Patients in Japan and the U.S.

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OBJECTIVE—Approximately 25% of patients who undergo percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) have diabetes, and the diagnosis of diabetes roughly doubles the mortality risk associated with coronary artery disease. However, the impact of diabetes may differ according to ethnicity. Our objective was to examine the impact of diabetes on long-term survival among U.S. and Japanese patients who underwent PCI or CABG.

RESEARCH DESIGN AND METHODS—For the current analysis, we included 8,871 patients from a Japanese multicenter registry (Coronary Revascularization Demonstrating Outcome database in Kyoto; median follow-up 3.5 years; interquartile range [IQR] 2.6–4.3) and 7,229 patients from a U.S. multipractice registry (Texas Heart Institute Research Database; median follow-up 5.2 years; IQR 3.8–6.5).

RESULTS—Diabetes was more prevalent among Japanese than U.S. patients (39.2 vs. 31.0%; $P < 0.001$). However, after revascularization, long-term all-cause mortality was lower in diabetic Japanese patients than in diabetic U.S. patients (85.4 vs. 82.2%; log-rank test $P = 0.009$), whereas it was similar in nondiabetic Japanese and U.S. patients (89.1 vs. 89.5%; $P = 0.50$). The national difference in crude mortality was also significant among insulin-using patients with diabetes (80.8 vs. 74.9%; $P = 0.023$). When long-term mortality was adjusted for known predictors, U.S. location was associated with greater long-term mortality risk than Japanese location among nondiabetic patients (hazard ratio 1.58 [95% CI 1.32–1.88]; $P < 0.001$) and, especially, diabetic patients (1.88 [1.54–2.30]; $P < 0.001$).

CONCLUSIONS—Although diabetes was less prevalent in U.S. patients than in Japanese patients, U.S. patients had higher overall long-term mortality risk. This difference was more pronounced in diabetic patients.

Coronary revascularization procedures are an important component of an integrated treatment paradigm for diabetic patients with coronary artery disease (CAD). Diabetes is found in roughly 25% of patients who undergo coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI) for CAD. It is noteworthy that a concomitant diagnosis of diabetes doubles the mortality

risk associated with CAD (1). This increased risk is thought to be due to the tendency of patients with diabetes to have a more diffuse and generalized form of atherosclerosis than patients without diabetes (2–4).

A high volume of CABG and PCI procedures are performed in both Japan and the U.S. The ethnicities and lifestyles of CAD patients differ greatly in different parts of the world (5,6), and one study report states that cardiovascular event rates among stable and ambulatory CAD patients are lower in Japan than in Western countries (7). These differences demonstrate the varying importance of different clinical risk factors among genetically and environmentally distinct populations.

One such factor is diabetes. Little is known about the clinical presentation and postrevascularization outcomes of Asian diabetic patients with CAD or how these patients compare with their counterparts in the U.S. Therefore, we sought to assess the clinical characteristics and long-term outcomes of diabetic patients in two different parts of the world (Japan and the U.S.) and performed a direct comparison of two large databases concerning PCI and CABG in these two countries.

RESEARCH DESIGN AND METHODS

—We evaluated the clinical characteristics and outcomes of diabetic patients in the Coronary Revascularization Demonstrating Outcome database in Kyoto (CREDO-Kyoto) and the Texas Heart Institute Research Database (THIRDBase). CREDO-Kyoto was a multicenter ($n = 29$) registry maintained in Kyoto, Japan, and THIRDBase is an ongoing single-center registry maintained at the Texas Heart Institute. The details of the design of CREDO-Kyoto and THIRDBase have been reported previously (8). Both of these comprehensive, longitudinal clinical registries of patients undergoing coronary revascularization procedures were designed to evaluate associated periprocedural and late events. Patients were enrolled in CREDO-Kyoto between 2000 and 2002, whereas THIRDBase has been a continuous, ongoing registry since 1993.

In the current analysis, we included THIRDBase patients enrolled between 1999 and 2003 so as to match the total number of patients in the CREDO-Kyoto registry. The resulting cohort comprised 16,100 patients: 8,871 patients from the CREDO-Kyoto registry (median follow-up period 3.5 years; interquartile range 2.6–4.3) and 7,229 patients from the THIRDBase registry (median follow-up period 5.2 years; interquartile range 3.8–6.5). Diabetes was defined as the presence of any indicator of diabetes in the registry data. In THIRDBase, these indicators were a prior clinical diagnosis of diabetes, a fasting blood glucose level of >7.0 mmol/L, and the use of antidiabetes agents; CREDO-Kyoto used these same indicators and also a glycated hemoglobin (HbA_{1c}) level of ≥6.9%. The value for HbA_{1c} (%) is estimated as an NGSP equivalent value (%) and is calculated by the formula HbA_{1c} (%) = HbA_{1c} (JDS)(%) + 0.4%, where JDS is the Japan Diabetes Society and considering the relational expression of HbA_{1c} (JDS)(%) measured by the previous Japanese standard substance and measurement methods and HbA_{1c} (NGSP) (9).

Our patient cohort included 5,697 patients (35.4%) with diabetes, with 3,473 (39.1%) from CREDO-Kyoto and 2,224 (30.7%) from THIRDBase. In both countries, all the study patients underwent initial, elective, isolated revascularization procedures. All PCI patients underwent placement of a bare-metal stent; drug-eluting stents were not available during the study period. Patients were excluded if they had had a previous PCI, required concomitant valve surgery or peripheral vascular revascularization, or were undergoing primary PCI for an acute myocardial infarction (MI).

Patient histories were obtained by means of an interview when the patient arrived at the hospital or clinic, and the details were entered into the database. The following variables were documented: left ventricular ejection fraction, number of diseased vessels, urgency of the revascularization procedure, presence of hypertension (characterized by a blood pressure of >130/90 mmHg for THIRD-Base and >140/90 for CREDO, or current use of antihypertensive medications), severity of angina (Canadian Cardiovascular Society classification), severity of congestive heart failure (New York Heart Association [NYHA] functional status), family history of CAD, previous MI, renal function, need for hemodialysis, and presence of peripheral vascular disease (occlusive or aneurysmal vascular disease in the aorta or in peripheral vessels).

Coronary anatomic and procedural characteristics, in-hospital outcomes, and vital status as of 31 December 2006 were assessed for all patients. For THIRDBase, survivorship was determined from the U.S. Department of Vital Statistics Database. For CREDO-Kyoto, follow-up data were obtained from hospital charts or by contacting patients or referring physicians. Both registries had remarkably high follow-up completion rates (THIRDBase: 100%; CREDO-Kyoto: 98% at 1 year and 95% at 2 years). Survival analyses included both in-hospital and long-term survival data, and these survival rates were not considered separately.

The use of data from THIRDBase was approved by the institutional review board at St. Luke's Episcopal Hospital (home of the Texas Heart Institute). Written informed consent was obtained from all enrollees at hospital admission. All analyzed data were stripped of personal identifiers. For CREDO-Kyoto, because of the retrospective nature of enrollment, written informed consent was not obtained from the patients; however, when later contacted for follow-up evaluation, 73 patients were excluded from the analysis because of their refusal to participate in the study. This process is concordant with the guidelines for epidemiologic studies issued by the Ministry of Health, Labor, and Welfare of Japan.

Statistical analysis

We stratified patients according to their location (U.S. or Japan) and whether they had diabetes. We assessed the patients' demographic characteristics by using the Pearson χ^2 test for discrete variables and the Student t test for continuous variables. We then used the Kaplan-Meier method to draw survival curves and the log-rank test to identify significant differences in unadjusted survival rates for patients with and without diabetes and for patients with and without insulin use. We also compared the two registries with respect to survival rates among patients who underwent PCI versus CABG.

Multivariable Cox proportional hazards models were constructed to control for possible confounding factors affecting the association between patient location and outcomes separately for diabetic and nondiabetic patients. The variables included in the multivariable model were age ≥65, sex, obesity, history of MI, heart failure, NYHA functional class, peripheral vascular disease, renal function, hypertension, hyperlipidemia, family history of CAD, smoking, the number of diseased vessels, and the geographic location of the registry. Renal function was categorized by a serum creatinine level of ≤179 μmol/L, a serum creatinine level of >179 μmol/L without hemodialysis, and a serum creatinine level of >179 μmol/L with hemodialysis. Cerebrovascular disease was excluded from the multivariable analyses because there were considerable differences in the way it was defined in each registry.

To assess the validity of the proportional hazards assumption, we plotted −log (−log [survival]) curves for each category of a nominal or ordinal covariate versus log (analysis time). Because the proportional hazards assumption did not hold for the mode of coronary revascularization, we applied the stratified Cox proportional hazards model, using revascularization procedure (CABG or PCI) as the stratification variable. To evaluate any differences in the effects of patient location on diabetic versus nondiabetic patients, we constructed a multivariable Cox model that included diabetes and an interaction term between diabetes and patient location, as well as the variables listed above.

Because the subjects were not assigned randomly to their respective locations, the association between location and outcome may result from unmeasured covariates that are associated with both exposure and outcome. Therefore, a sensitivity analysis was performed to investigate how the findings of the multivariable analysis may be affected by certain variations in the assumptions about an unmeasured binary confounder (10).

Analyses were performed by using STATA 9.2 software (StataCorp, College Station, TX). All tests of significance were two-tailed, and $P < 0.05$ was considered significant.

RESULTS—Characteristics of the diabetic and nondiabetic patients are described in Table 1. Japanese patients were older and were more likely to be male. U.S. patients were more likely to be obese, having a higher mean BMI. In general, U.S. patients also had a higher prevalence of coronary risk factors (hypertension, dyslipidemia, and family history), MI, heart failure, and other atherosclerotic diseases (cerebrovascular and peripheral vascular). Multivessel disease was more common in Japanese patients than in U.S.

Table 1—*Demographic data of diabetic patients stratified by registry and revascularization procedure*

Variable	Missing data (n)	Japanese patients	U.S. patients	P value	PCI Japanese patients	PCI U.S. patients	PCI P value	CABG Japanese patients	CABG U.S. patients	CABG P value
n		3,473	2,224		2,373	1,110		1,100	1,114	
Age (years)	0	66.7 (9.3)	62.5 (10.3)	<0.001	66.6 (9.7)	62.2 (10.6)	<0.001	66.8 (8.5)	62.9 (10.0)	<0.001
Women	0	31.8	35.8	0.002	31.7	38.0	<0.001	32.0	33.6	0.43
BMI (kg/m^2)	0	23.8 (3.3)	30.7 (6.3)	<0.001	24.0 (3.4)	31.4 (6.6)	<0.001	23.4 (3.2)	30.0 (5.9)	<0.001
CABG	0	31.7	50.1	<0.001						
History of MI	7	29.1	35.6	<0.001	25.9	33.5	<0.001	36.0	37.7	0.41
History of heart failure	12	19.7	21.8	0.061	15.6	17.9	0.077	28.7	25.6	0.1
NYHA functional class IV	12	2.2	11.6	<0.001	2.5	9.6	<0.001	1.7	13.5	<0.001
Peripheral vascular disease	5	14.4	18.5	<0.001	9.7	14.3	<0.001	24.7	22.6	0.26
Cerebrovascular disease	4	18.8	7.3	<0.001	16.3	6.0	<0.001	24.3	8.6	<0.001
Valve disease	9	6.7	7.6	0.21	7.0	7.1	0.91	6.1	8.1	0.07
Renal insufficiency	42	9.7	17.0	<0.001	8.9	17.2	<0.001	11.4	16.9	<0.001
Hemodialysis	0	5.6	2.7	<0.001	5.2	3.4	0.019	6.3	2.0	<0.001
Hypertension	2	70.9	84.8	<0.001	70.9	85.1	<0.001	70.9	84.5	<0.001
Dyslipidemia	8	53.0	64.6	<0.001	52.7	66.4	<0.001	53.6	62.8	<0.001
Family history of CHD	190	15.2	31.7	<0.001	14.7	32.3	<0.001	16.5	31.2	<0.001
Smoking	69	50.1	41.6	<0.001	49.9	39.3	<0.001	50.7	43.8	0.001
Insulin-treated diabetes	0	21.6	22.0	0.7	18.6	20.2	0.28	28.0	23.9	0.027
Diseased vessels	282			<0.001			<0.001			<0.001
1		25.8	40.5		34.9	62.6		6.0	18.2	
2		33.2	35.9		37.5	29.6		23.8	42.3	
3		41.0	23.6		27.6	7.8		70.2	39.5	

Data are % or mean (SD) unless otherwise indicated. CHD, coronary heart disease.

patients. The aforementioned trends were also seen when the PCI and CABG patients were analyzed separately, except that Japanese CABG patients had a higher prevalence of peripheral vascular disease than U.S. CABG patients.

The unadjusted survival rate was significantly better in Japanese patients than in U.S. patients in the diabetic subgroup (85.4 vs. 82.2%; log-rank test P = 0.009), whereas unadjusted survival was similar between Japanese and U.S. patients in the nondiabetic subgroup (89.1 vs. 89.5%; P = 0.50) (Fig. 1A and B). Survival rates also favored Japanese patients among both insulin-using and non–insulin-using diabetic patients (80.8 vs. 74.9%; P = 0.023) (Fig. 1C and D). Furthermore, Japanese patients in the diabetic subgroup had higher survival rates than their U.S. counterparts regardless of the modality of coronary revascularization (P = 0.008 [diabetic patients] and 0.71 [nondiabetic patients] for PCI, P = 0.69 [diabetic patients] and 0.24 [nondiabetic patients] for CABG).

The predictors of all-cause mortality are listed in Table 2. After adjustment, both diabetic and nondiabetic U.S. patients had a significantly greater risk for death than their Japanese counterparts. However, the effect size was greater in the diabetic patients than in the nondiabetic patients (hazard ratio [HR] 1.88 [95% CI 1.54–2.30] and 1.58 [1.32–1.88], respectively). Furthermore, a statistically significant interaction was seen between diabetes and patient location. The HR was 1.16 (1.002–1.35) for diabetes, 1.51 (1.29–1.77) for U.S. location, and 1.33 (1.09–1.62) for the interaction term in the multivariable model.

Table 3 shows the results of the sensitivity analysis with the point and interval estimates for the HR of the interaction term. Let Φ denote the probability ratio of U.S. patients with diabetes and the relative hazard of death associated with the unmeasured binary confounder. Let PR denote the prevalence of the unmeasured confounder. Under $\Phi = 1.5$, the point and

interval estimate will always remain >1. Under $\Phi = 2.0$, the lower limit of the 95% CI will be <1 if $0.2 \leq PR \leq 0.6$. In other words, the true relative hazard of U.S. patients with diabetes will be misinterpreted, over a range of plausible values (0.2 to 0.6) for the prevalence of the confounder only if there is a confounder with $\Phi = 2.0$.

CONCLUSIONS—In the current study, we evaluated the impact of diabetes in two large-scale CAD registries. The greater prevalence of diabetes in Japanese patients is in accordance with the rates of this disease recorded by other CAD registries in Japan (11). The long-term mortality rate was significantly lower in Japanese patients than in U.S. patients, particularly in the diabetic subgroups. For the nondiabetic patients, crude mortality did not differ between the two groups. However, the two registries differed greatly with respect to patients' clinical backgrounds; Japanese patients were older, more likely
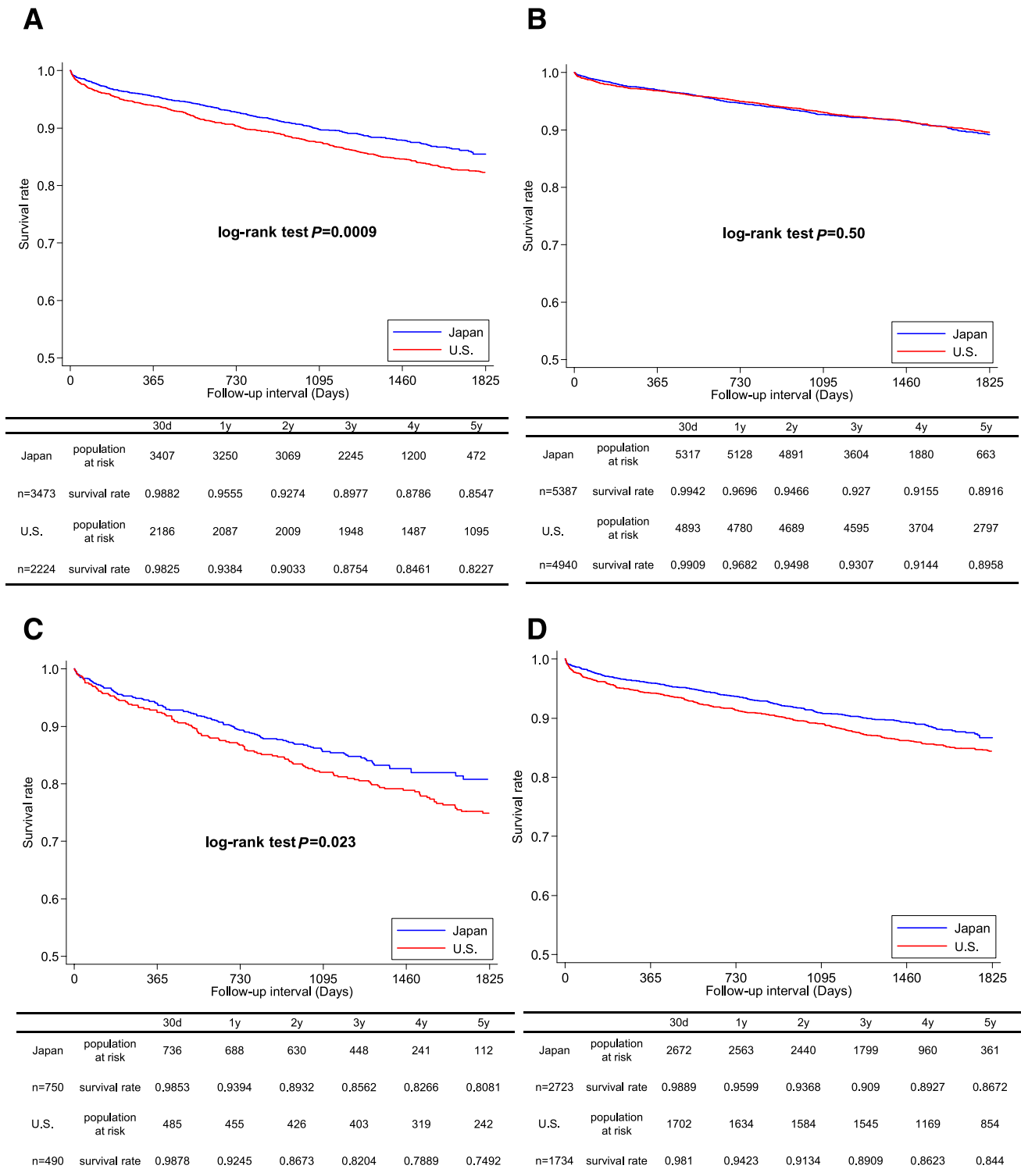
Figure 1—*Kaplan-Meier survival curves for patients with diabetes* (A), *patients without diabetes* (B), *insulin-treated patients* (C), *and non–insulin-treated patients* (D). *D, day; Y, year.*

to be smokers, and more likely to have dyslipidemia. In contrast, the American patients were more likely to be obese and had a higher prevalence of atherosclerotic diseases, such as MI, peripheral vascular disease, and renal insufficiency.

When adjusted for these clinical variables, U.S. location was a significant risk factor for mortality, although it was not as strong a predictor of mortality as diabetes.

The results of the sensitivity analysis provide additional insights into our findings

and support our conclusion that U.S. location—through race, lifestyle, or both—increases the risk of mortality of diabetic patients after revascularization. Because of the effort made to identify and adjust for all the known risk factors, it is unlikely

Table 2—Results of multivariate analysis for patients with and without diabetes

Variable	Diabetes		Nondiabetes	
	HR (95% CI)	P value	HR (95% CI)	P value
Age ≥65 years	2.372 (2.011–2.798)	<0.001	2.981 (2.510–3.539)	<0.001
Female	1.063 (0.904–1.251)	0.458	1.032 (0.885–1.202)	0.689
Obesity (≥25 m/kg^2)	0.689 (0.578–0.822)	0.000	0.658 (0.564–0.767)	<0.001
History of MI	1.051 (0.898–1.230)	0.533	1.323 (1.149–1.524)	<0.001
History of heart failure	1.835 (1.529–2.201)	<0.001	2.300 (1.942–2.724)	<0.001
NYHA functional class IV	1.220 (0.946–1.572)	0.126	1.168 (0.891–1.530)	0.261
Peripheral vascular disease	1.397 (1.175–1.661)	<0.001	1.674 (1.420–1.973)	<0.001
Renal function				
Serum creatinine ≤179 μmol/L	1.000		1.000	
Serum creatinine >179 μmol/L	2.599 (2.128–3.175)	<0.001	1.964 (1.572–2.454)	<0.001
Hemodialysis	5.179 (4.108–6.530)	<0.001	5.637 (4.295–7.397)	<0.001
Hypertension	1.276 (1.046–1.557)	0.016	1.173 (1.001–1.373)	0.048
Hyperlipidemia	0.870 (0.748–1.012)	0.072	0.628 (0.546–0.722)	<0.001
Family history of CHD	0.837 (0.691–1.014)	0.069	0.868 (0.733–1.027)	0.099
Smoking	1.103 (0.941–1.291)	0.226	1.226 (1.064–1.414)	0.005
Diseased vessels				
1	1.000		1.000	
2	1.240 (1.023–1.504)	0.029	1.047 (0.888–1.234)	0.587
3	1.436 (1.165–1.770)	0.001	1.437 (1.190–1.735)	<0.001
U.S. location	1.886 (1.544–2.304)	<0.001	1.583 (1.328–1.887)	<0.001

CHD, coronary heart disease.

that an unmeasured binary confounder with an HR of 1.5 or 2.0 exists, even though these were the values considered in the analysis.

Patients who have both CAD and diabetes have a poor long-term outcome, especially when multiple vessels are involved. Coronary artery lesions in diabetic patients are frequently complex owing to these lesions' small size and diffuse involvement with atherosclerosis. These features necessitate the use of longer stents during percutaneous treatment, and they increase the rate of complications during CABG. These effects of diabetes tended to be worse in U.S. patients; in our study, the impact of diabetes was consistently stronger in U.S. patients than in Japanese patients

Table 3—Results of sensitivity analysis of the interaction between diabetes and patient location

PR	Φ = 1.5			Φ = 2.0		
	PR$_1$	PR$_0$	rHR (95% CI)	PR$_1$	PR$_0$	rHR (95% CI)
0.1	0.14	0.09	1.30 (1.07–1.59)	0.18	0.09	1.22 (1.00–1.49)
0.2	0.27	0.19	1.28 (1.05–1.56)	0.33	0.18	1.18 (0.96–1.44)
0.3	0.39	0.29	1.27 (1.04–1.55)	0.46	0.27	1.16 (0.95–1.42)
0.4	0.50	0.38	1.27 (1.04–1.55)	0.57	0.37	1.16 (0.95–1.42)
0.5	0.60	0.48	1.27 (1.04–1.55)	0.67	0.47	1.18 (0.96–1.44)
0.6	0.69	0.59	1.28 (1.05–1.56)	0.75	0.58	1.20 (0.98–1.46)
0.7	0.78	0.69	1.29 (1.06–1.57)	0.82	0.68	1.23 (1.01–1.50)
0.8	0.86	0.79	1.30 (1.07–1.59)	0.89	0.79	1.26 (1.03–1.54)
0.9	0.93	0.90	1.32 (1.08–1.60)	0.95	0.89	1.29 (1.06–1.58)

Φ, probability ratio of U.S. patients with diabetes and relative hazard of death associated with the unmeasured binary confounder; PR, prevalence of the unmeasured confounder; PR$_1$, prevalence of the unmeasured confounder among U.S. patients with diabetes; PR$_0$, prevalence of the unmeasured confounder among Japanese or nondiabetic patients; rHR, relative hazard of death for U.S. patients with diabetes.

in all analyzed subgroups regardless of insulin use, procedure type (PCI or CABG), and the number of diseased vessels.

The outcome of cardiovascular diseases in patients with diabetes is known to be better in the Japanese population. Other large-scale registries have also shown a difference in the incidence of CAD-related clinical events among patients in different countries, highlighting higher mortality rates in North American populations and lower mortality rates in Japanese and Chinese populations (12,13). A multicenter j-Cypher registry in Japan showed a greater adjusted risk of serious cardiovascular events in diabetic patients, particularly those using insulin, than in patients without diabetes (14). It is notable that the risk of serious cardiovascular events for the patients with non–insulin-treated diabetes was similar to that for the patients without diabetes, which is in contrast with the findings from Western studies. Although the precise mechanism for better outcomes in Japanese patients is unclear, it may be that Japanese patients with diabetes have a lower degree of hyperinsulinemia and insulin resistance than Western patients with diabetes (15,16). This difference might also be reflected in the higher prevalence of heart failure, peripheral arterial disease, and chronic kidney disease in U.S. patients. Furthermore, diet and lifestyle seem to play an important role. A number of dietary differences remain, such as a high intake of fish and salt (Japan) versus red meat and sugar (U.S.). Both the observational studies and randomized trials have shown a benefit of fish consumption on risk of CAD (17,18).

Our study has several limitations. First, statistical adjustments were made only for patient characteristics for which data were available in both registries. However, we used information from two well-established registries, and the study involved a large number of patients (>8,000), a high rate of clinical follow-up, and an excellent database infrastructure and support system. Furthermore, our sensitivity analysis showed that an unmeasured confounder with only modest effects would not drop the lower confidence limit to <1. Still, there remains a possibility that more subtle, immeasurable variables, such as differences in physician attitudes and approaches to diagnosis, as well as health policies and social and cultural circumstances, may have some impact and require further study. Second, technologic advances may quickly outdate our findings. One such advance is the advent

of drug-eluting stents, which have dramatically reduced the need for repeat revascularization after stent placement. There is not yet any clear-cut evidence, however, that such stents improve survival (19). Therefore, we may still draw valid inferences about comparative survival from patients who receive bare-metal stents. Last, THIRDBase did not include information on individual antidiabetes medications and HbA_{1c} level, so we were not able to stratify the analysis by these factors.

Although U.S. patients had a lower prevalence of diabetes than Japanese patients, the U.S. patients had a higher overall long-term mortality risk, and this difference was more pronounced in diabetic patients. These results were consistent among patients who underwent PCI or CABG and when only insulin-treated diabetes was considered. These findings may have important implications for applying the results of Western clinical studies to Asian patients. Further study is needed to establish ideal revascularization strategies for Asian patients.

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