

Predicting Macro- and Microvascular Complications in Type 2 Diabetes

The Japan Diabetes Complications Study/the Japanese Elderly Diabetes Intervention Trial risk engine

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OBJECTIVE—To develop and validate a risk engine that calculates the risks of macro- and microvascular complications in type 2 diabetes.

RESEARCH DESIGN AND METHODS—We analyzed pooled data from two clinical trials on 1,748 Japanese type 2 diabetic patients without diabetes complications other than mild diabetic retinopathy with a median follow-up of 7.2 years. End points were coronary heart disease (CHD), stroke, noncardiovascular mortality, overt nephropathy defined by persistent proteinuria, and progression of retinopathy. We fit a multistate Cox regression model to derive an algorithm for prediction. The predictive accuracy of the calculated 5-year risks was cross-validated.

RESULTS—Sex, age, HbA_{1c}, years after diagnosis, BMI, systolic blood pressure, non-HDL cholesterol, albumin-to-creatinine ratio, atrial fibrillation, current smoker, and leisure-time physical activity were risk factors for macro- and microvascular complications and were incorporated into the risk engine. The observed-to-predicted (O/P) ratios for each event were between 0.93 and 1.08, and Hosmer-Lemeshow tests showed no significant deviations between observed and predicted events. In contrast, the UK Prospective Diabetes Study (UKPDS) risk engine overestimated CHD risk (O/P ratios: 0.30 for CHD and 0.72 for stroke). C statistics in our Japanese patients were high for CHD, noncardiovascular mortality, and overt nephropathy (0.725, 0.696, and 0.767) but moderate for stroke and progression of retinopathy (0.636 and 0.614). By combining macro- and microvascular risks, the classification of low- and high-risk patients was improved by a net reclassification improvement of 5.7% ($P = 0.02$).

CONCLUSIONS—The risk engine accurately predicts macro- and microvascular complications and would provide helpful information in risk classification and health economic simulations.

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Risk classification for vascular complications is of particular importance in diabetes care, and there is a need for validated diabetes-specific risk engines (1,2). Asian populations account for >60% of the world's diabetes patients (3,4), but data used for most of the engines specific to diabetes include only a limited number of Asians (5–9). Asian patients with diabetes have several important features. We previously reported that Japanese patients have a markedly low prevalence of obesity and low incidence rates of overt nephropathy and diabetic retinopathy (10–13). Furthermore, the risk factor profiles of diabetes complications are quite different between Japanese and Western subjects with diabetes (14). In cohort studies of multiple ethnic groups, lower incidence rates of cardiovascular disease (CVD) were observed in Asian patients than in whites (15,16). Given the overestimation of risks of coronary heart disease (CHD) and stroke in Chinese patients by the UK Prospective Diabetes Study (UKPDS) risk engine (17,18), risk engines for non-Asian populations may not be transportable to Asian patients. To our knowledge, only the Hong Kong Diabetes Registry (HKDR) has developed risk engines for Asian patients with diabetes (17–20).

Most risk engines have focused on classical cardiovascular risk factors such as control of HbA_{1c}, blood pressure, and lipids (5–9,17–20), but, increasingly, studies have suggested the importance of lifestyle factors. In fact, exercise has been shown to reduce all-cause mortality (21,22) and is encouraged by guidelines for type 2 diabetes (23,24). A recent survey of general practitioners in Germany indicated that those physicians thought that to be useful, risk engines should link estimated risks with appropriate recommendations for lifestyle changes (25). Another concern is the lack of capacity to assess multiple diseases simultaneously (25). However, just combining the results of risk engines specific to each vascular complication may yield biased estimates

of absolute risks since it is likely that each engine was developed independently, and a correlation between incidences of vascular complications is not accounted for in the development process.

Data from the 1,748 patients with type 2 diabetes in the Japan Diabetes Complications Study (JDCS) (26) and the Japanese Elderly Diabetes Intervention Trial (J-EDIT) (27) provide an opportunity to develop a comprehensive risk engine for Asian patients with type 2 diabetes. The aim of the current study was therefore to develop and validate an algorithm that separately calculates each risk of the first occurrence for five events: fatal and nonfatal CHD, fatal and nonfatal stroke, noncardiovascular mortality, overt nephropathy, and progression of retinopathy. This was done by fitting a multistate Cox regression model (28), an extension of the Cox model to multiple time-to-event end points, to the pooled data from these trials.

RESEARCH DESIGN AND METHODS

Patients and measurements

Design of the JDCS and the J-EDIT has been described in detail elsewhere (26,27). In the JDCS, 2,033 Japanese type 2 diabetes patients 40–70 years of age whose HbA_{1c} levels were $\geq 7.0\%$ were randomized to a conventional treatment group and a lifestyle intervention group; throughout the paper, we present the National Glycohemoglobin Standardization Program value of HbA_{1c} calculated as follows: $0.25 + 1.02 \times \text{JDC value}$ (29). The latter group received education on lifestyle modification by telephone counseling and at each outpatient clinic visit in addition to usual care. The J-EDIT is a randomized, controlled trial of intensive and conventional treatments for diabetes that registered a total of 1,173 Japanese type 2 diabetes patients 65–85 years of age whose HbA_{1c} levels were $\geq 8.1\%$, or $\geq 7.5\%$ with at least one of the following criteria: BMI $\geq 25 \text{ kg/m}^2$; blood pressure $\geq 130/85 \text{ mmHg}$; serum total cholesterol $\geq 200 \text{ mg/dL}$ (5.17 mmol/L) or LDL cholesterol $\geq 120 \text{ mg/dL}$ (3.10 mmol/L) in participants without CHD; serum total cholesterol $\geq 180 \text{ mg/dL}$ (4.65 mmol/L) or LDL cholesterol $\geq 100 \text{ mg/dL}$ (2.59 mmol/L) in participants with CHD; triglycerides $\geq 150 \text{ mg/dL}$ (1.68 mmol/L); and HDL cholesterol $< 40 \text{ mg/dL}$ (1.03 mmol/L). The protocols of the JDCS and J-EDIT received approval from the ethical committees of all of the

participating institutes, and written informed consent was obtained from all patients before enrollment. The present analysis excluded patients who had any history of angina pectoris, myocardial infarction, stroke, peripheral artery disease, familial hypercholesterolemia (diagnosed clinically by markedly elevated LDL cholesterol levels with enlarged Achilles tendons and/or family history of premature coronary artery disease), type III hyperlipidemia (diagnosed by broad β -band on electrophoresis), nephrotic syndrome, serum creatinine levels $> 1.3 \text{ mg/dL}$ ($120 \mu\text{mol/L}$), mean values of two spot urine examinations for an albumin excretion rate of $150 \text{ mg/g creatinine}$ (17.0 mg/mmol) or more, microscopic hematuria, or other clinical findings indicating other renal diseases, preproliferative and proliferative retinopathy, and major ocular disease (e.g., glaucoma, dense cataract, or history of cataract surgery). Baseline data were collected for demographics, results of clinical examinations, laboratory measurements performed at local laboratories, and lifestyle factors such as dietary content and smoking status determined by self-reported questionnaires. Leisure-time physical activity (LTPA) was also assessed at baseline by a self-administered questionnaire, which was almost identical to that used and validated in the Health Professionals' Follow-up Study (30). The patients were asked to report their average frequency (times/week) and duration (min/time) of normal walking, brisk walking, jogging, golfing, tennis, swimming, aerobics dancing, cycling, and other miscellaneous exercise as specified by each patient. The duration engaged in each activity in min/time was multiplied by that activity's typical energy expenditure, expressed in metabolic equivalents (METs), and overall activities were summed to yield a MET/h score per week (31). Data management was conducted by a central data center. Follow-up data were collected through a standardized annual report from each investigator. Non-HDL cholesterol (NHDLC) levels were calculated by total cholesterol subtracted by HDL cholesterol. LDL cholesterol levels were calculated using the Friedewald formula, that is, NHDLC subtracted by triglycerides divided by 5 if triglyceride levels are $< 400 \text{ mg/dL}$ (4.48 mmol/L); otherwise, LDL cholesterol levels were treated as missing data.

End points

End points were five time-to-event variables: fatal or nonfatal CHD, fatal

or nonfatal stroke, noncardiovascular mortality, overt nephropathy defined by persistent proteinuria, and progression of retinopathy since randomization. The definitions of the events have been described in detail elsewhere (12,13,27,32). In brief, diabetic retinopathy was determined annually by qualified ophthalmologists at each institute using the international diabetic retinopathy and diabetic macular edema disease scales (33) with minor modification: stage 0, no retinopathy; stage 1, hemorrhage and hard exudates; stage 2, soft exudates; stage 3, intraretinal microvascular abnormalities and venous changes, including beading, loop, and duplication; and stage 4, new vessels, vitreous hemorrhage, fibrous proliferation, and retinal detachment. A retinopathy event was progression to stage 3 or 4. A nephropathy event was defined as the development of overt nephropathy (spot urinary albumin excretion $> 33.9 \text{ mg/mmol creatinine}$ in two consecutive samples) (12). Macrovascular events included the occurrence of fatal and nonfatal definite CHD (angina pectoris or myocardial infarction) and fatal and nonfatal stroke. The diagnosis of angina pectoris and myocardial infarction was according to criteria defined by the Multinational Monitoring of Trends and Determinants in Cardiovascular Disease project, and diagnosis of stroke was according to guidelines defined by the Ministry of Health, Labour, and Welfare of Japan (32). Adjudication of end points was performed by central committees comprised of experts in each complication based on additional data such as those obtained by computed tomography or magnetic resonance imaging of the brain or sequential changes in electrocardiograms.

Statistical analysis

The JDCS/J-EDIT (JJ) risk engine calculates each risk of the first occurrence within a user-specified time point for the five events described above. The occurrences of these events are viewed as transitions between disease states and were modeled by a multistate model that follows the Markov renewal process (28). The disease states and transitions assumed in the multistate model are detailed in Supplementary Data. We fit a multistate model using a standard procedure for the stratified Cox regression model. That is, we assumed that baseline intensities for any of the transitions were possibly different but that transition intensities to a disease state share common

hazard ratios (HRs) for risk factors. The following risk factors were screened through a backward variable selection with the critical value of $P = 0.1$: age, sex, HbA_{1c}, years after diagnosis, BMI, systolic blood pressure (SBP), NHDLC, LDL cholesterol, HDL cholesterol, log-transformed triglycerides, log-transformed urine albumin-to-creatinine ratio (ACR), estimated glomerular filtration rate, atrial fibrillation, smoking status, alcohol intake, and LTPA. BMI was categorized by cutoff points of 18.5 and 25 kg/m². LTPA was categorized by the cutoff point of 3.8 METs-h/week, which corresponds to the intensity of home activity or conditioning exercise (31). HRs in this model were estimated by maximizing the partial likelihood, and then baseline intensity functions were calculated by the Breslow estimator. Missing data were substituted using the multiple imputation method.

We assessed the predictive accuracy of the 5-year risks based on the JJ risk engine using 10-fold cross-validation, i.e., we performed 10 rounds of cross-validation using different partitions. One round of cross-validation involved randomly partitioning a sample of data on 1,748 patients into complementary subsets, fitting the stratified Cox regression model to one subset of 90% of patients, and validating the model on the remaining subset with the criteria described below. We compared hazards

for end points between tertiles of the calculated 5-year risks from the 10-fold cross-validation by the Cox regression. Calibration, namely, how closely the prediction reflected observed events, was assessed for each event by the Hosmer-Lemeshow test and the mean of observed-to-predicted (O/P) ratios, which was calculated as the mean of ratios of the observed-to-expected events across the strata used in the Hosmer-Lemeshow test. Discrimination, the ability to distinguish between those who experienced the event and those who did not, was evaluated using Harrell C statistics, the proportion of all patient pairs in which the predictions of the model and observed events were concordant. Further, we constructed a reclassification table of macro- and microvascular complications (34).

All analyses were conducted by the central data center with the use of SAS software version 9.2 (SAS Institute, Cary, NC). The authors had full access to the data and take responsibility for their integrity. All reported P values for statistical tests are two tailed, and $P < 0.05$ was taken to indicate statistical significance.

RESULTS—The mean \pm SD (range) age and HbA_{1c} level at baseline of the 1,748 Japanese type 2 diabetic patients was 62.1 \pm 8.6 (40–84) years and 7.9 \pm 1.2 (6.0–15.8)%, respectively, and 49.9%

of the subjects were women. Their mean baseline values indicated that the subjects had good control of weight (BMI = 23.2 \pm 3.1 kg/m²; waist circumference = 80.3 \pm 9.6 cm), blood pressure (SBP = 132.9 \pm 16.0 mmHg), and serum cholesterol levels (NHDLC = 3.78 \pm 0.90 mmol/L; LDL cholesterol = 3.16 \pm 0.82 mmol/L; HDL cholesterol = 1.43 \pm 0.44 mmol/L; triglycerides = 1.39 \pm 0.88 mmol/L). Their baseline ACR levels were quite low, with a median \pm IQR of 1.8 \pm 3.0 mg/mmol, as we excluded those with ACR of 17.0 g/mmol or more. Current smokers and past smokers accounted for 24.4 and 24.0%, respectively, of patients. The median (IQR) LTPA at baseline was 10.5 (1.6–22.5) METs-h/week, and 34.0% of patients had no exercise habit (<3.8 METs-h/week). During the median follow-up of 7.2 years, among the 1,748 subjects, we observed 96 (5.5%) events of fatal or nonfatal CHD, 89 (5.1%) fatal or nonfatal strokes, 71 (4.1%) overt nephropathies defined by persistent proteinuria, and 64 (3.7%) noncardiovascular deaths. Of the 1,297 patients without retinopathy at baseline, 415 (32.0%) developed retinopathy. Of the 866 patients who had retinopathy or developed retinopathy after baseline, 113 (13.0%) had progression to retinopathy of stage 3 or 4.

The backward variable selection procedure identified 11 baseline risk factors

Table 1—HRs of risk factors incorporated in the best-fitting multistate Cox regression model

	CHD				Stroke				Noncardiovascular mortality			
	HR	95% CI		P	HR	95% CI		P	HR	95% CI		P
Sex (woman/man)	0.41	0.24	0.70	<0.01	0.46	0.29	0.73	<0.01	0.55	0.29	1.04	0.07
Age (+10 years)	1.38	1.02	1.85	0.04	1.55	1.17	2.06	<0.01	2.44	1.70	3.50	<0.01
HbA _{1c} (+1%)	1.22	1.02	1.45	0.03	1.23	1.04	1.44	0.02				
BMI (<18.5/18.5–25 kg/m ²)									3.22	1.40	7.37	0.01
BMI (\geq 25/18.5–25 kg/m ²)									1.16	0.60	2.21	0.66
SBP (+10 mmHg)	1.13	0.98	1.31	0.10	1.16	1.00	1.33	0.045				
NHDLC (+1 mmol/L)	1.56	1.26	1.93	<0.01	1.38	1.10	1.74	0.01				
Atrial fibrillation (yes/no)					12.48	3.77	41.29	<0.01				
Current smoker (yes/no)	1.67	1.00	2.81	0.052					2.11	1.04	4.26	0.04
LTPA (\geq 3.8/<3.8 METs-h/week)					0.63	0.39	1.01	0.053	0.57	0.33	1.01	0.054
	Overt nephropathy				Retinopathy							
Age (+10 years)					1.16	1.04	1.30	0.01				
HbA _{1c} (+1%)	1.28	1.08	1.53	0.01	1.32	1.25	1.40	<0.01				
Years after diagnosis (+1 years)					1.04	1.03	1.06	<0.01				
BMI (<18.5/18.5–25 kg/m ²)					0.67	0.43	1.03	0.07				
BMI (\geq 25/18.5–25 kg/m ²)					1.22	0.99	1.49	0.06				
SBP (+10 mmHg)	1.14	0.97	1.33	0.11								
Log ACR (+1 unit)	3.02	2.16	4.23	<0.01	1.11	1.01	1.22	0.03				
Atrial fibrillation (yes/no)	5.54	0.74	41.49	0.10								
Current smoker (yes/no)	2.18	1.28	3.71	<0.01								

for macro- and microvascular complications and noncardiovascular mortality. Table 1 shows the HRs, 95% CIs, and P values for these risk factors. Significant modifiable risk factors were HbA_{1c} and NHDL-C for CHD, HbA_{1c}, SBP, and NHDL-C for stroke, BMI <18.5 kg/m² and being a current smoker for noncardiovascular mortality, HbA_{1c} and being a current smoker for overt nephropathy, and HbA_{1c} for retinopathy. Having an exercise habit was associated with reduced risks of stroke and mortality, although with only borderline statistical significance. All of the risk factors that were retained through the variable selection procedure were incorporated into the JJ risk engine. The algorithm of the JJ risk engine is described in Supplementary Data.

The performance of the JJ risk engine was evaluated by several validation criteria. Tertile Cox regression showed that the 5-year risks calculated by the JJ risk engine effectively classified populations at low and high risk for each complication. The HRs (95% CI) of the second and third tertiles compared with the first tertile were 2.09 (1.07–4.09) and 5.22 (2.84–9.58) for CHD; 1.78 (0.96–3.30) and 3.32 (1.86–5.92) for stroke; 2.14 (1.09–4.18) and 3.17 (1.65–6.09) for noncardiovascular mortality; 1.54 (0.55–4.34) and 10.59 (4.56–24.59) for overt nephropathy; and 1.18 (0.58–2.40) and 2.56 (1.37–4.81) for progression of retinopathy.

Table 2 shows the predictive accuracy of the JJ risk engine regarding calibration and discrimination. The O/P ratios for each complication, including noncardiovascular mortality, ranged between 0.93 and 1.08, and Hosmer-Lemeshow tests did not show any significant deviations between the observed and predicted events. In contrast, the UKPDS risk engine (5,6) overestimated CHD risk in Japanese patients (O/P ratios [Hosmer-Lemeshow P]: 0.30 [P < 0.01] for CHD and 0.72 [P = 0.54] for stroke) (Table 2). Discrimination according to C statistics was high for CHD, noncardiovascular mortality, and overt nephropathy (0.696–0.767) but was moderate for stroke and progression of retinopathy (0.636 and 0.614).

Table 3 compares risk classification by the 5-year risk of macrovascular disease based on the JJ risk engine with that based on the UKPDS risk engine. By the UKPDS risk engine, more than half of patients had a macrovascular risk of 10% or more (249 of the 376 cases and 697

Table 2—Predictive accuracy of the JJ risk engine in 1,748 patients

	Calibration			Discrimination		
	Mean predicted 5-year risk	Observed 5-year risk	O/P ratio	P†	C statistic	95% CI
CHD	2.70%	2.92%	1.08	0.14	0.725	0.656–0.793
By the UKPDS risk engine	(9.66%)	—	(0.30)	(<0.01)	(0.695)	(0.626–0.764)
Stroke	3.36%	3.26%	0.97	0.12	0.636	0.564–0.708
By the UKPDS risk engine	(4.52%)	—	(0.72)	(0.54)	(0.638)	(0.566–0.711)
Noncardiovascular mortality	2.08%	2.12%	1.02	0.12	0.696	0.613–0.778
Overt nephropathy	2.28%	2.40%	1.04	0.11	0.767	0.690–0.845
Progression of retinopathy*	10.96%	10.20%	0.93	0.13	0.614	0.524–0.705

*Patients without diabetes retinopathy at baseline were excluded. †The Hosmer-Lemeshow test with eight degrees of freedom. P < 0.05 indicates significant deviation between predicted and observed events.

of the 1,372 noncases), as expected by the tendency of overestimation. The sensitivity and specificity of the UKPDS risk engine with a cutoff value of 10% risk were 66.2 and 49.2%, respectively. In contrast, only 101 of the 376 cases (26.9%) who developed any of the events had a macrovascular risk of 10% or more based on the JJ risk engine, yielding sensitivity of 26.9% and specificity of 89.1%.

Table 4 shows how the combination of 5-year risks of macro- and microvascular complications based on the JJ risk engine classified low-risk and high-risk patients. If we combined macro- and microvascular risks, 73 of 376 cases (19.4%) and 187 of 1,372 noncases (13.6%) were newly classified as a high-risk population, and sensitivity increased up to 46.3% while specificity was maintained at 75.4%. The net reclassification

improvement (total of sensitivity and specificity in this case) was improved by 5.7% (P = 0.02).

To illustrate the use of the JJ risk engine, consider two Japanese men 60 years of age with simple diabetic retinopathy and without atrial fibrillation who do not have smoking and exercise habits. The clinical characteristics of both patients are HbA_{1c} = 9%, duration of diabetes = 20 years, BMI = 23 kg/m², NHDL-C = 3.88 mmol/L, and ACR = 6.79 mg/mmol creatinine. The SBP of one patient is 120 mmHg. His leading risk is estimated to be the progression of retinopathy (5-year risk, 15.5%), and his macrovascular risks are moderate (9.2% for CHD and 9.6% for stroke). His 5-year risks of noncardiovascular death and overt nephropathy are low (4.8 and 3.7%, respectively). The other patient has

Table 3—Risk classification of the 1,748 patients according to 5-year risks of macrovascular disease based on the JJ risk engine and the UKPDS risk engine

5-Year risk by the UKPDS risk engine*	5-Year risk by the JJ risk engine*					Total	
	<5%	5–10%	10% or more				
Patients who developed events							
<5%	37	9.8%	2	0.5%	0	0.0%	39
5–10%	66	17.6%	19	5.1%	3	0.8%	88
10% or more	37	9.8%	114	30.3%	98	26.1%	249
Total	140		135		101		376
Patients who did not develop any events							
<5%	245	17.9%	7	0.5%	0	0.0%	252
5–10%	341	24.9%	78	5.7%	4	0.3%	423
10% or more	202	14.7%	349	25.4%	146	10.6%	697
Total	788		434		150		1,372

*Data are n and percent. Probability of any occurrence of CHD or stroke within 5 years.

Table 4—Risk classification of the 1,748 patients according to 5-year risks of macro- and microvascular diseases based on the JJ risk engine

5-Year risk of microvascular disease†	5-Year risk of macrovascular disease*						Total
	<5%	5–10%	10% or more				
Patients who developed events							
<5%	79	21.0%	48	12.8%	19	5.1%	146
5–10%	40	10.6%	35	9.3%	20	5.3%	95
10% or more	21	5.6%	52	13.8%	62	16.5%	135
Total	140		135		101		376
Patients who did not develop any events							
<5%	601	43.8%	215	15.7%	40	2.9%	865
5–10%	115	8.4%	104	7.6%	34	2.5%	240
10% or more	72	5.2%	115	8.4%	76	5.5%	267
Total	759		434		150		1,372

*Data are n and percent. Probability of any occurrence of CHD or stroke within 5 years. †Probability of any occurrence of overt nephropathy defined by persistent proteinuria or progression of retinopathy within 5 years.

an SBP of 180 mmHg. His leading risks are macrovascular diseases (16.1% for CHD and 17.6% for stroke), and his microvascular risks are moderate (7.8% for nephropathy and 13.6% for retinopathy). The risk of noncardiovascular mortality is estimated to be 4.0%.

CONCLUSIONS—In this study, we developed a novel risk engine that integrates modifiable lifestyle and clinical risk factors, including HbA_{1c}, BMI, SBP, NHDLC, current smoking, and LTPA into the risks of a first occurrence of macro- and microvascular complications. We confirmed that the risk engine performed reasonably well and that combining macro- and microvascular risks improved the classification of low-risk and high-risk patients by a net reclassification improvement of 5.7%. In contrast, the UKPDS risk engine overestimated CHD risk, and this tendency is consistent with a previous report in Asian patients (18). A web application for the JJ risk engine, which works in both Windows and Macintosh environments, is available at <http://www.biostatistics.jp/prediction/jjre>.

With the advent of modern therapeutics, especially hypoglycemic and antihypertensive agents, the early identification of high-risk patients is an appealing strategy (35). A novelty of the JJ risk engine is that it allows risk classification based on the risk not only of CVD but also of renal and eye diseases. Although the prevalence of micro- or macroalbuminuria in Asian hypertensive diabetes is alarmingly high (36), most of the progression to overt nephropathy occurs in a small fraction of patients with elevated HbA_{1c} and SBP values

and a smoking habit (12). In this study, patients in the fourth quartile of the calculated risk developed overt nephropathy at a rate 10 times greater than those in the first quartile. Most risk engines are specific to CVD; however, greater emphasis should be placed when assessing risk among diabetic patients given that diabetic nephropathy and retinopathy are major causes of ESRD and blindness, respectively. Combining macro- and microvascular risks resulted in the net reclassification improvement of 5.7% ($P = 0.02$) and a sensitivity and specificity of 46.3 and 75.4%, respectively; only 16.5% of cases were classified as the high-risk population for macro- and microvascular diseases and only 43.8% of noncases were in the low-risk population (Table 4). Thus, the discriminatory power of the JJ risk engine was only moderate, despite the statistically significant improvement in prediction, and exploring novel risk factors would be of particular importance for more accurate risk classification.

The JJ risk engine shares features similar to those with previously developed risk engines. The predictors of CHD are the same as in the UKPDS risk engine (5) except for the inclusion of NHDLC instead of the total cholesterol-to-HDL cholesterol ratio. Donnan et al. (7) added diabetes duration, treated hypertension, height, and two interaction terms into their model, and the risk equation of the HKDR includes diabetes duration, estimated glomerular filtration rate, and ACR additionally but does not use HbA_{1c} (18). A recent cohort study in Japan also

suggested that the progression of the albuminuria stage is a risk factor of CVD (37). In contrast, log ACR was not associated with CHD or stroke in our study. This discordant observation would be attributable to the exclusion of low microalbuminuria in our study. The elevation of ACR within a range of normoalbuminuria may not lead to an increase in the risk of CVD. We also found that the UKPDS risk engine overestimated CHD risk (Table 2) and the C statistic of the JJ risk engine (0.725) was slightly higher than that of the risk equation of the HKDR (0.704) (18), indicating that the JJ risk engine may outperform the previously developed risk engines for the prediction of CHD. For the prediction of stroke, we did not identify smoking status and years after diagnosis as predictors, which are included in the UKPDS risk engine (6). The risk equation from the Swedish National Diabetes Register incorporates the use of antihypertensive drugs and lipid-lowering drugs as predictors (9). However, medical therapies are not considered in the current analysis, since the effects of medications on vascular complications were likely to be confounded by other clinical factors. In contrast to CHD, the C statistic of the JJ risk engine (0.636) was similar to the UKPDS risk engine (0.638) and lower than the risk equation of the HKDR (0.749) (17). With regard to lifestyle factors, we identified LTPA as a risk factor for stroke and noncardiovascular mortality, although the statistical significance was borderline. On the other hand, BMI, which has been recognized as one of the most important risk factors in the deterioration of type 2 diabetes, was not associated with CVD. We previously reported that the BMI of Japanese patients is much lower than that of white patients, although in those reports, other patient characteristics were similar in terms of age, HbA_{1c}, and daily energy intake (10,11). Our findings run contrary to the results of studies of white patients, but data on diet in diabetic patients are sparse, particularly in Asia. In this study, the contribution of lifestyle factors to the risk assessment appears to be limited, and the associations between lifestyle and diabetes complications are worthy of further research.

One important feature of this study is that we analyzed pooled data from two nationwide clinical trials in Japan. The end points were defined similarly in both trials and follow-up was performed by diabetes specialists, ensuring data of relatively high quality. Patients generally

had fair or good glycemic, weight, blood pressure, and lipid control. The major difference between the two trials was eligible age, i.e., age between 40 and 70 years in the JDCS and age between 65 and 85 years in the J-EDIT. Prior to pooling the datasets, we compared important clinical factors between patients in the two trials and found no notable differences except for age; therefore, pooling of the datasets was considered to be valid. Consequently, the study population in the present analysis included subjects spanning several decades, i.e., those from 40 to 84 years. This can be expected to enhance the generalizability of the algorithm.

Statistical modeling can be much more complex if we handle multiple events simultaneously. To the best of our knowledge, this is the first study that applies a multistate model to the construction of a risk engine. It is notable that these events are not inherently independent and the JJ risk engine calculates each probability of the first occurrence for five events. Thus, if the risk of an event (e.g., overt nephropathy) was increased by a risk factor (e.g., log ACR), the probability of the first occurrence of other events (e.g., stroke) can decrease theoretically even if there are no direct associations with the risk factor.

Several limitations warrant mention. First, transportability of prognostic information is critical, but in this study we evaluated only the internal validity. Thus, external validation is required in other populations. Second, updating the algorithm by long-term follow-up data or pooled analysis with other studies in Asia is desirable given that the size of our cohort is relatively small and the observed events of CVD and overt nephropathy in this population were relatively few. Third, we included angina pectoris and transient ischemic attack as components of the cardiovascular events, although they are soft end points. Consequently, the JJ risk engine would provide macrovascular risks higher than those by other risk engines based on only hard cardiovascular events. Fourth, data on peripheral arterial disease and hemoglobin levels were not available. These factors were included as inputs into the HKDR all-cause mortality risk score (19), and peripheral arterial disease is a clinically relevant cardiovascular outcome. Fifth, the use of aspirin, which might increase the risk of hemorrhagic stroke, was not investigated. Finally, we defined overt nephropathy as the presence of persistent proteinuria, since an elevated

urinary albumin excretion due to nondiabetic renal lesions or conditions is not rare.

In conclusion, the risk engine allowed accurate and comprehensive risk assessment of macro- and microvascular complications, although external validation is required in other populations. The calculated absolute risks of vascular complications can be used in risk classification for individual patients, health economic simulations, and estimation of the burden of the disease.

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Sh.T., Sa.T., and Y.O. performed statistical analysis and wrote the manuscript. S.I. managed data. H.Y., S.K., Y.A., N.Y., A.A., H.I., and H.S. planned and conducted the JDCS and the J-EDIT. H.S. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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