Risk of Cardiovascular Diseases Is Increased Even with Mild Diabetic Retinopathy

The Japan Diabetes Complications Study

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Objective: Diabetic retinopathy (DR) is linked to cardiovascular risk in diabetic patients. This study examined whether mild-stage DR is associated with risk of coronary heart disease (CHD) and stroke in type 2 diabetic patients of the Japan Diabetes Complications Study (JDCS).

Design: Prospective cohort study.

Participants: In the JDCS, there were 2033 Japanese persons with type 2 diabetes free of cardiovascular diseases at baseline.

Methods: Diabetic retinopathy was ascertained from clinical and photographic grading (70%) following the international clinical diabetic retinopathy and diabetic macular edema disease severity scales. Incident CHD and stroke were followed up prospectively annually up to 8 years.

Main Outcome Measures: Eight-year incidence of CHD and stroke compared between persons with or without DR.

Results: After adjusting for traditional cardiovascular risk factors, persons with mild to moderate nonproliferative DR had a higher risk of CHD (hazard ratio [HR], 1.69; 95% confidence interval [CI], 1.17–2.97) and stroke (HR, 2.69; 95% CI, 1.03–4.86). Presence of retinal hemorrhages or microaneurysms was associated with risk of CHD (HR, 1.63; 95% CI, 1.04–2.56) but was not associated with stroke (P = 0.06). Presence of cotton-wool spots was associated with risk of incident stroke (HR, 2.39; 95% CI, 1.35–4.24) but was not associated with CHD (P = 0.66). When information about DR was added in the prediction models for CHD and stroke based on traditional cardiovascular risk factors, the area under the receiver operating curve improved from 0.682 to 0.692 and 0.640 to 0.677, and 9% and 13% of persons were reclassified correctly for CHD and stroke, respectively.

Conclusions: Type 2 diabetic patients with even a mild stage of DR, such as dot hemorrhages, are already at higher risk of CHD and stroke independent of traditional risk factors.

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Diabetic retinopathy (DR) is estimated to affect approximately 100 million people worldwide when extrapolated to the world diabetes population in 2010.[1] Increasing DR severity is associated with an increased risk of vision loss and risk of vision-threatening proliferative disease over time.[2,3] Presence of DR is not only one of the most common microvascular complications of diabetes, it also is an established predictor of cardiovascular diseases (CVDs). Diabetic patients with DR have been reported to be at higher risk of incident stroke[4–7] and coronary heart disease (CHD).[4,5,8] Kramer et al[9] reported that persons with any degree of DR are at 61% higher risk of CVD events and all-cause mortality independent of traditional risk factors based on the meta-analysis data of 20 epidemiologic studies.

However, there is limited knowledge regarding whether this association is observed consistently in Asian populations.[10,11] Sasaki et al[10] reported an association between the presence of any stage of DR and all-cause mortality in a Japanese type 2 diabetic cohort; detailed association between DR severity and specific CVD outcomes of stroke and CHD is unclear. Considering that duration of diabetes and glucose control or other risk factors are associated with severity of DR,[1] it is reasonable to speculate that people with a severe stage of microvascular complications such as advanced DR have macrovascular complications of CVD. What remains less understood is whether milder stage DR is associated with increased risk of CHD and stroke. There have been limited data reporting associations of early stage of DR and CVD and, if such as association exists, whether there is a continuous association between severity of DR and risk of CVD.[7,12]

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Table 1. Baseline Characteristic of the 1620 Patients Included in the Analysis Compared with Those Who Were Excluded

Characteristic	Included (n = 1620)		Excluded (n = 413)		P Value
	Mean	*Standard Deviation*	*Mean*	*Standard Deviation*	
Age (yrs)	58.3	7.0	59.5	6.8	<0.01
Women (%)	46.4		47.0		0.84
HbA1c (%)	7.9	1.3	7.9	1.2	0.92
Fasting blood sugar (mg/dl)	160.2	43.7	159.6	41.8	0.81
Years after diagnosis	10.6	7.0	11.9	8.0	<0.01
Weight (kg)	58.6	9.4	59.2	9.6	0.20
BMI, kg/m^2 (%)	23.0	3.0	23.3	3.0	0.11
<18.5	5.5		4.4		0.36
≥25	24.3		27.2		0.23
Systolic blood pressure (mmHg)	131.2	16.3	133.7	16.2	<0.01
Diastolic blood pressure (mmHg)	76.7	9.9	77.4	10.3	0.23
Total cholesterol (mg/dl)	200.9	33.9	203.6	38.7	0.16
LDL cholesterol (mg/dl)	122.3	31.8	123.3	34.6	0.58
HDL cholesterol (mg/dl)	54.7	16.7	54.1	17.1	0.51
Triglyceride* (mg/dl)	101.5	73.0	109.0	83.0	0.02
Treated by insulin (%)	20.0		24.3		0.06
Current smoker (%)	28.3		25.8		0.35

BMI = body mass index; HbA1c = glycosylated hemoglobin; HDL = high-density lipoprotein; LDL = low-density lipoprotein.
*Geometric mean.

Whether the presence or severity of DR is associated with CVD independent of traditional cardiovascular factors also is important to understand the potential usefulness of DR information as additional information to improve CVD prediction. Therefore, this study examined associations between the presence and severity of DR and risk of 8-year incident CHD, stroke, and combined outcome of any CVD in the Japanese Diabetes Complications Study (JDCS).

Table 2. Baseline Clinical Characteristics of Type 2 Diabetes Patients in the Japan Diabetes Complications Study

Characteristics	Persons without Diabetic Retinopathy (n = 1141)	Persons with Mild Nonproliferative Diabetic Retinopathy (n = 412)	Persons with Moderate Nonproliferative Diabetic Retinopathy (n = 67)	P Value (for Trend)
Age (yrs)	58.2 (6.9)	58.6 (7.0)	58.0 (7.0)	0.54
Women (%)	44.9	50.5	47.8	0.10
HbA1c (%)	7.8 (1.3)	8.0 (1.2)	8.2 (1.3)	<0.01
Fasting glucose (mmol/l)	8.9 (2.4)	8.9 (2.5)	8.9 (2.2)	0.90
Duration of diabetes (yrs)	9.7 (6.8)	12.7 (7.0)	13.1 (6.5)	<0.01
Insulin treated (%)	15.5	28.9	43.9	<0.01
Oral hypoglycemic agents (%)	64.1	69.9	68.7	0.05
BMI (kg/m^2)	23.0 (3.0)	23.1 (3.0)	22.8 (3.1)	0.85
<18.5 (%)	5.8	4.6	6.0	0.55
≥25 (%)	24.9	23.1	22.4	0.41
Systolic blood pressure (mmHg)	130.4 (16.2)	132.7 (16.5)	136.4 (16.4)	<0.01
Diastolic blood pressure (mmHg)	76.8 (10.1)	76.3 (9.3)	77.4 (10.3)	0.82
LDL cholesterol (mmol/l)	3.19 (0.82)	3.09 (0.81)	3.19 (0.94)	0.12
HDL cholesterol (mmol/l)	1.40 (0.42)	1.45 (0.43)	1.51 (0.52)	<0.01
Triglycerides (mmol/l)*	1.15 (0.82)	1.09 (0.81)	1.12 (0.50)	0.02
Current smoker (%)	29.8	23.7	32.8	0.18
Physical exercise (kilocalories/day)	143.5 (267.5)	117.4 (265.8)	91.9 (288.0)	0.16
Spot urine ACR (mg/gCr)	15.3 (25.0)	19.2 (42.3)	25.2 (75.7)	<0.01
Retinopathy lesions				
Dot/blot retinal hemorrhages (%)	*	88.1/32.9	93.8/78.1	—
Hard exudates (%)	*	0	1.0	—
Cotton-wool spots (%)	*	32.6	62.5	—

ACR = albumin-to-creatinine ratio; BMI, body mass index; HbA1c = glycosylated hemoglobin; HDL = high-density lipoprotein; LDL, low-density lipoprotein.
Data shown as mean ± standard deviation unless otherwise indicated.
*Geometric mean (1 standard deviation).

Table 3. Cox Regression Analysis of the 1620 Type 2 Diabetic Japanese Patients for Diabetic Retinopathy and Cardiovascular Diseases

	Coronary Heart Disease			Stroke			Any Cardiovascular Disease		
	*Hazard Ratio**	*95% Confidence Interval*	*P Value*	*Hazard Ratio**	*95% Confidence Interval*	*P Value*	*Hazard Ratio**	*95% Confidence Interval*	*P Value*
Age (+1 yr)	1.03	1.00–1.07	0.08	1.07	1.03–1.11	<0.01	1.06	1.03–1.09	<0.01
Women (vs. men)	0.60	0.37–0.96	0.03	0.73	0.42–1.25	0.25	0.57	0.38–0.85	0.01
HbA1c (+1%)	1.10	0.93–1.30	0.27	1.15	0.96–1.38	0.14	1.16	1.02–1.33	0.03
Duration of diabetes (+1 yr)	1.02	0.99–1.05	0.12	0.97	0.94–1.01	0.15	1.00	0.97–1.02	0.84
BMI (+1 kg/m^2)	1.03	0.95–1.12	0.48	1.01	0.92–1.10	0.86	1.02	0.95–1.09	0.67
Systolic blood pressure (+1 mmHg)	1.02	1.00–1.03	0.04	1.02	1.00–1.03	0.04	1.02	1.00–1.03	0.01
LDL cholesterol (+0.025 mmol/l)	1.01	1.01–1.02	<0.01	1.00	0.99–1.01	0.53	1.01	1.00–1.01	<0.01
HDL cholesterol (+0.025 mmol/l)	1.00	0.99–1.02	0.61	1.00	0.98–1.02	0.84	1.00	0.99–1.01	1.00
Log triglycerides (+1 unit)	2.41	1.52–3.83	<0.01	1.22	0.72–2.07	0.46	1.94	1.32–2.84	<0.01
Log ACR (+1 unit)	0.97	0.80–1.16	0.72	0.97	0.79–1.19	0.78	0.93	0.79–1.08	0.32
Current or past smoker (vs. never smoked)	1.86	1.17–2.97	0.01	1.42	0.81–2.47	0.22	1.67	1.13–2.46	0.01
Presence of DR	1.69	1.09–2.63	0.02	1.69	1.03–2.80	0.04	1.92	1.33–2.75	<0.01

ACR = albumin-to-creatinine ratio; BMI = body mass index; DR = mild to moderate nonproliferative diabetic retinopathy; HbA1c = glycosylated hemoglobin; HDL = high-density lipoprotein; LDL = low-density lipoprotein.
*Hazard ratios of multivariate model with listed variables.

Patients and Methods

Study Participants

The detailed study design and protocol of the JDCS have been described elsewhere.[13,14] In brief, the JDCS is a multicenter, open-labeled, randomized trial of type 2 diabetic patients examining the impact of lifestyle intervention on diabetic complications. In 1996, 2033 adults Japanese persons (age range, 40–70 years) with type 2 diabetes whose hemoglobin A1c (HbA1c) levels were 6.5% or more were enrolled and randomized; primary outcome analyses have been reported elsewhere.[13] After excluding patients with a known history of CVD and familial hypercholesterolemia and those without baseline assessment of DR, 1620 patients were included in this analysis. Persons included in this analysis were younger, had a shorter duration of diabetes, had a lower systolic blood pressure, and had a lower triglyceride level compared with those who were excluded from the current analysis (Table 1). This study was performed in accordance with the Declaration of Helsinki and received ethical approval from the institutional review boards; all participants gave written informed consent. This study is a subanalysis of the JDCS, which has been registered with identifier C000000222 in a trial registry (www.umin.ac.jp; accessed February 13, 2012).

Assessment of Diabetic Retinopathy

Ophthalmologists who have a subspecialty and experience in retinal diseases at each study site determined the pathologic features related to DR by mydriatic indirect ophthalmoscopic examination and slit-lamp biomicroscopic fundus examination using a precorneal lens. Supplemental information from fundus photography and fluorescein angiography were allowed to be used as needed. A standardized paper-based grading form was used to record individual lesions of DR (e.g., microaneurysms or dot hemorrhages, blot hemorrhages, hard exudates, cotton-wool spots, venous beading, intraretinal microvascular abnormalities, retinal neovascularization, and other proliferative changes). At each visit, ophthal-

Table 4. Cox Regression Analysis of the 1620 Type 2 Diabetic Japanese

	Coronary Heart Disease			
	Crude Incidence Rate per 1000 Person-Years	*Hazard Ratio**	*95% Confidence Interval*	*P Value*
Severity of DR				
No DR	7.54	1	Reference	
Mild nonproliferative DR	12.46	1.62	1.02–2.58	0.04
Moderate nonproliferative DR	13.61	2.18	0.92–5.17	0.08
P value for trend			0.01	
DR lesions				
Retinal hemorrhages (dot or blot) or microaneurysms (present vs. absent)		1.63	1.04–2.56	0.03
Hard exudates (present vs. absent)		1.83	0.78–4.25	0.16
Cotton-wool spots (present vs. absent)		1.15	0.62–2.14	0.66

DR = diabetic retinopathy.
*Adjusted for age, sex, hemoglobin A1c, duration of diabetes, body mass index, systolic blood pressure, low-density lipoprotein cholesterol,

mologists filled in the grading form and sent them with retinal images (macula-centered and disc-centered image or centered between the fovea and disc if wide photographic angle was 45° or 50°). Standardized images could be obtained from 1424 of 2033 patients (70%). However, because standardized retinal images could not be obtained (e.g., different camera type, different format of film or digital, and different photographic angles) in the remaining 30% of the participants, a clinical diagnosis of the presence and severity of DR based on the standardized form provided by ophthalmologists was used when retinal images were not available. Severity of DR was categorized following the international clinical diabetic retinopathy severity scales into 5 categories: no retinopathy (equivalent to the Early Treatment of Diabetic Retinopathy Study [ETDRS] scale level 10), mild nonproliferative DR (equivalent to ETDRS level 20), moderate nonproliferative DR (equivalent to ETDRS levels 35, 43, and 47), severe nonproliferative DR (equivalent to ETDRS levels 53A–53E), and proliferative DR (PDR; equivalent to ETDRS levels 61 or higher).[15] To assess consistency in detecting and classifying DR solely based on clinical examination, a random sample was selected and the assessment was cross-validated by ophthalmologists on site using a centralized assessment. The grading agreement on the status of DR was cross-validated; the weighted κ statistics for the agreement of DR severity of 5 categories was 0.59 (95% confidence interval [CI], 0.54–0.65) and was considered to be more than moderate.[14] Persons with severe nonproliferative DR or worse were excluded from this study because the primary outcome of this study was to investigate the occurrence of DR and progression of DR from mild nonproliferative DR to severe nonproliferative DR or nonproliferative DR.[10,11] A history of ocular diseases and surgeries also was surveyed; persons with significant cataract or other ocular diseases confounding the diagnosis of DR were excluded.[14]

Patients were assessed for CHD and stroke at baseline and annually for up to 8 years. Information regarding CVD outcomes was collected from death certificates, hospital admission or discharge records, community health centers, medicolegal records, general practitioners, and interviews with patients and relatives, in addition to electrocardiogram records and laboratory records. Fatal and nonfatal CHD and stroke events were identified during follow-up and were certified by at least 2 members of the experts' committee who were masked to subjects' characteristics and the other member's diagnosis. Myocardial infarction and CHD were defined according to the World Health Organization (WHO) Monitoring of Trends and Determinants in Cardiovascular Disease criteria.[16] In brief, the diagnosis of CHD was based on clinical symptoms, electrocardiography electrocardiography findings, cardiac enzymes, necropsy findings, and history of CHD. In all subjects at risk, a 12-lead electrocardiogram was recorded at each assessment. Angina pectoris was defined as typical effort-dependent chest pain or oppression relieved at rest or by using nitroglycerin, as validated by exercise-positive electrocardiography, angiography, or both. A patient with a first percutaneous coronary intervention or coronary artery bypass graft also was considered to have a CHD event.

Stroke events were defined as a constellation of focal or global neurologic deficits of sudden or rapid onset and for which there was no apparent cause other than a vascular accident, as determined by a detailed history, a neurologic examination, and ancillary diagnostic procedures such as computed tomography, magnetic resonance imaging, cerebral angiography, and lumbar puncture. Stroke events were classified as cerebral infarction (including embolus), intracranial hemorrhage (including subarachnoid hemorrhage), transient ischemic attack, or stroke of undetermined type in accordance with WHO criteria.[17] Cases of asymptomatic lesions detected by brain imaging (i.e., silent infarction) were not included. Only a first-ever event during the study period was counted for the analysis; "any CVD" was defined as "either CHD or stroke," or as "one having developed earlier event if patients had experienced both events."

Statistical Analysis

The Kaplan-Meier method was used to plot a survival curve for incidence of CVD. The Cox proportional hazard model was used to estimate hazards ratios (HRs) associated with the presence or absence of DR at baseline examination adjusting for age, sex, HbA1c level, duration of diabetes, body mass index, systolic blood pressure, low-density lipoprotein (LDL) cholesterol level, high-density lipoprotein cholesterol level, log triglycerides, log albumin-to-creatinine ratio, and smoking. The same adjustment factors were used to estimate HRs for the severity of DR (i.e., no DR vs. mild nonproliferative DR and no DR vs. moderate nonproliferative DR) and the presence or absence of individual DR lesions, namely dot hemorrhages, blot hemorrhages, hard exudates, and cotton-wool spots.

Then, changes in predictive accuracy were examined by adding DR information onto prediction by the traditional car-

Patients for Diabetic Retinopathy and Cardiovascular Diseases

Stroke				Any Cardiovascular Disease			
Crude Incidence Rate per 1000 Person-Years	*Hazard Ratio**	*95% Confidence Interval*	P *Value*	*Crude Incidence Rate per 1000 Person-Years*	*Hazard Ratio**	*95% Confidence Interval*	P *Value*
5.72	1	Reference		11.03	1	Reference	
9.50	1.64	0.98–2.76	0.06	18.70	1.86	1.28–2.71	<0.01
9.15	2.15	0.75–6.21	0.16	18.86	2.34	1.11–4.93	0.03
		0.03				<0.01	
	1.63	0.97–2.73	0.06		1.78	1.23–2.58	<0.01
	1.76	0.62–4.97	0.28		1.83	0.88–3.80	0.10
	2.39	1.35–4.24	<0.01		1.87	1.20–2.91	0.01

log triglycerides, log albumin-to-creatinine ratio, and smoking.

diovascular risk factors in the United Kingdom Prospective Diabetes Study (UKPDS) risk engine.[18,19] Changes in the area under the receiver operating characteristic curve (AUC) were examined by integrating the presence or absence of DR lesions with logistic regression models based on the UKPDS risk factors. Changes in reclassification capacity also were assessed by plotting a risk of CVD predicted by the UKPDS risk factors plus information regarding the presence or absence of DR lesions against the results predicted by the UKPDS risk factors alone. All *P* values were 2 sided. A *P* value less than 0.05 was considered statistically significant. Statistical analyses were carried out using the SAS software package version 9.2 (SAS Institute, Cary, NC).

Results

Of the 1620 patients, 412 (25.4%) and 67 (4.1%) had mild or moderate nonproliferative DR, respectively (Table 2). The cumulative number of CHD events in persons with mild nonproliferative DR and moderate nonproliferative DR were 35 (8.5%) and 6 (9.0%), respectively; the cumulative number of stroke events in persons with mild nonproliferative DR and moderate nonproliferative DR were 27 (6.6%) and 4 (6.0%), respectively.

Older age, male sex, higher HbA1c level, systolic blood pressure, LDL cholesterol level, triglycerides level, and smoking status were associated significantly with any CVD. Male sex, higher systolic blood pressure, LDL cholesterol level, triglycerides level, and smoking status were associated with a higher risk of CHD in the multivariate model. Older age and higher systolic blood pressure were associated with a higher risk of stroke (Table 3). Persons with any DR had a 1.69 times higher risk of both CHD and stroke ($P = 0.02$ and $P = 0.04$) and a 1.92 times higher risk of any CVD compared with persons without DR ($P<0.01$) after adjusting for age, sex, HbA1c level, duration of diabetes, body mass index, systolic blood pressure, LDL cholesterol level, high-density lipoprotein cholesterol level, log triglycerides, log albumin-to-creatinine ratio, and smoking status (Table 3). When the analyses were repeated to the confined subsample that had standardized retinal images with confirmed diagnosis based on central grading for DR, the associations between DR and stroke were consistently significant (adjusted HR, 1.86; 95% CI, 1.00–3.45; $P = 0.049$). However, the association with CHD was diminished to a nonsignificant level (adjusted HR, 1.34; 95% CI, 0.76–2.34; $P = 0.31$).

Persons with a mild or moderate stage of DR had higher risk of CHD, stroke, and any CVD ($P<0.01$ for trend, $P = 0.03$ for trend, and $P<0.01$ for trend, respectively; Table 4). Presence of retinal hemorrhages or microaneurysms was associated with up to approximately a 60% to 80% higher risk of CHD developing ($P = 0.03$) and any CVD ($P<0.01$; Table 4). Persons with hard exudates seem to have a higher risk of CHD, stroke, and any CVD, but these associations did not reach statistical significance. Presence of cotton-wool spots was associated with a more than 2-fold higher risk of incident stroke and an 87% higher risk of any CVD but not with CHD (Table 4).

With the model estimating risk of CHD based on traditional cardiovascular risks factors proposed by the UKPDS,[18] the AUC analysis improved from 0.682 in the model without DR (95% CI, 0.626–0.737; shown with light blue, Fig 1A) to 0.697 in the model with DR (95% CI, 0.641–0.752; shown with dark blue, Fig 1A). This difference did not reach statistical significance ($P = 0.22$). Figure 2A shows how adding DR information on the model with UKPDS risk factors reclassified CHD cases (n = 100, red dot) and noncases (n = 1520, blue dot). Reclassified correctly in the model including DR information were 6 cases (6%) and 53 noncases (3%); however, 6 cases (6%) and 63 noncases (4%) were reclassified in the model with DR incorrectly.

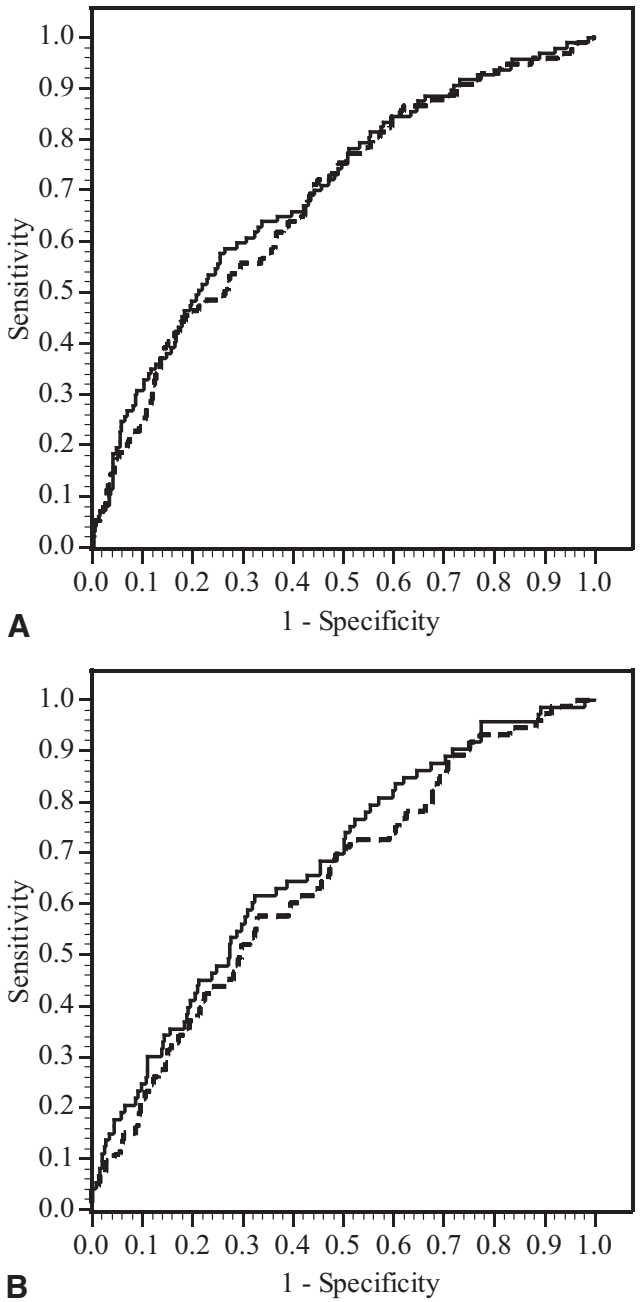

Figure 1. **A**, Graph showing a comparison of the receiver operating curves for coronary heart disease based on the United Kingdom Prospective Diabetes Study (UKPDS) risk factors with (solid line) or without (dashed line) diabetic retinopathy. **B**, Graph showing a comparison of receiver operating curves for stroke based on the UKPDS risk factors with (solid line) or without (dashed line) diabetic retinopathy.

For prediction of stroke, the AUC analysis improved from 0.640 (95% CI, 0.576–0.704; shown with dark blue, Fig 1B) to 0.677 (95% CI, 0.615–0.739; shown with light blue, Fig 1B) by adding DR information; again, this difference was not statistically significant ($P = 0.12$). As shown in Figure 2B, reclassification of stroke cases (n = 76, red dot) and noncases (n = 1544, blue dot)

was in favor of prediction with the model including DR; 9 cases (12%) and 1 noncase (1%) were reclassified correctly by adding DR to the prediction model, whereas 1 case (1%) and 55 noncases (4%) were reclassified by DR incorrectly.

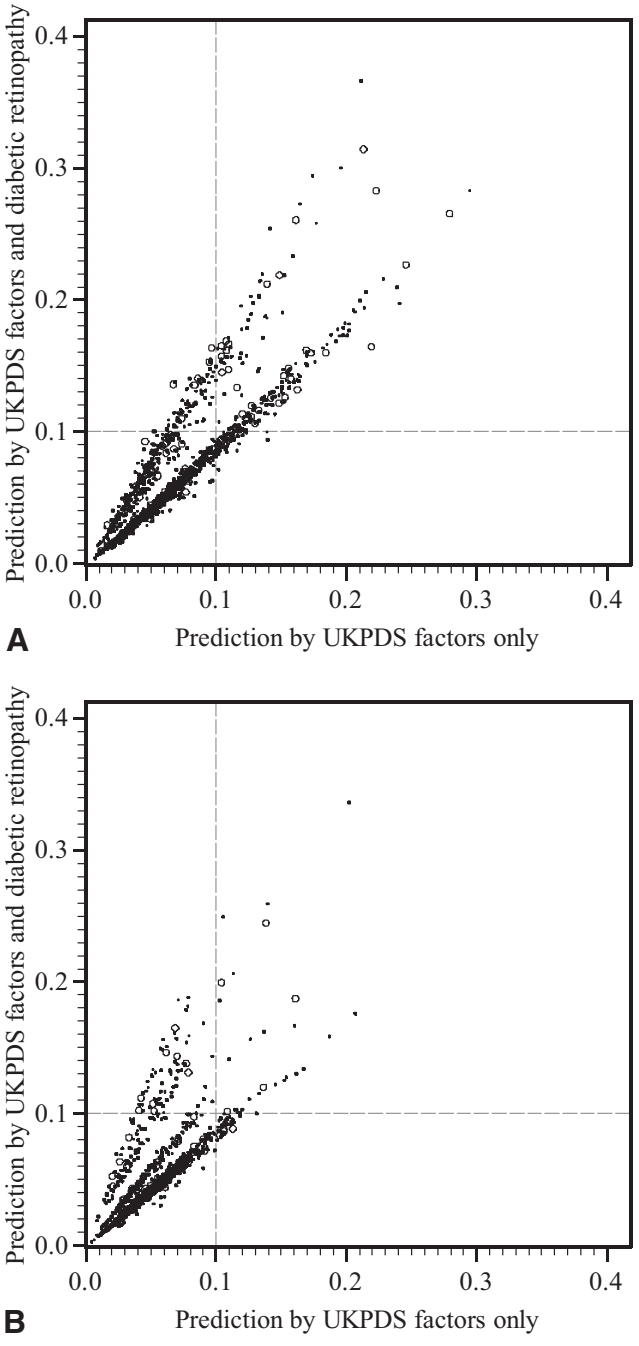

Figure 2. **A**, Graph showing the risk of coronary heart disease plotted for predicted risk by United Kingdom Prospective Diabetes Study (UKPDS) models with diabetic retinopathy against predicted risk by the UKPDS model without diabetic retinopathy. Reclassification of coronary heart disease is shown for cases (circles) and noncases (black dots). **B**, Graph showing reclassification of stroke cases (circles) and noncases (black dots) based on the UKPDS risk factors with or without diabetic retinopathy.

Discussion

This analysis of adult Japanese persons with type 2 diabetes found persons with even a mild stage DR already are at approximately at a 70% higher risk of developing CHD and stroke independent of cardiovascular risks. There were significant increasing trends for CHD, stroke, and any CVD by increasing severity stage of DR. Most importantly, these associations were confirmed to be significant after adjusting for traditional cardiovascular risk factors. The association between diabetic retinopathy and risk of developing CVD has been reported in multiple cohort studies.[4,5,7,8,12,20–23] In the Wisconsin Epidemiological Study of Diabetic Retinopathy, the presence of PDR was associated with incident stroke in both younger-onset and older-onset diabetes, independent of duration of diabetes, glucose level, and other risk factors.[4,12,23] In the WHO Multinational Study of Vascular Disease in Diabetes, this not only was confirmed, but also the findings showed that any level of DR was associated with incident stroke both in men and women with type 2 diabetes.[5] Severity of DR also was associated with risk of stroke in persons with type 1 diabetes.[12] Associations between milder stage of DR and stroke are controversial. In the Atherosclerosis Risk in Communities (ARIC) Study, the presence of nonproliferative DR was associated with a 2-fold increased risk of developing stroke in persons with type 2 diabetes.[7] Similarly, the ARIC study reported that the presence of DR is associated with a 2-fold increased risk of CHD and that the severity of DR was associated with increasing CHD risk.[8]

However, there has been limited knowledge from Asian populations.[10,11] This is important because there exist differences in the epidemiologic and risk associations of CVD between a white population and an Asian Japanese population.[24–26] For example, the incidence of stroke is much higher in Japanese persons than American Japanese persons in Hawaii.[27] For risk associations of CVD, this study showed a discrepancy in body mass indices between white and Japanese patients with type 2 diabetes (approximately 29 kg/m^2 in white patients from the UKPDS vs. 23 kg/m^2).[28] Another example is lipid profile and its association with CVD. Low-density lipoprotein cholesterol was the most important risk factor for CHD in both white and Asian populations, and the second most important risk in the cohort of the JDCS was the serum triglyceride level,[24,26] whereas lower high-density lipoprotein cholesterol was considered to be the second most important risk factor in the UKPDS.[24,26] Based on these differences in risk associations of CVD, there is a potential need for an ethnicity-specific risk prediction model of CVD (e.g., such as the ethnicity-specific metabolic syndrome and its component guideline as risk of CVD).[25,29] This study confirmed that the presence of DR is found consistently to be associated with an increased risk of stroke and CHD in Japanese persons with type 2 diabetes. Sasaki et al[10] reported an association between any stage of DR and all-cause mortality in a Japanese type 2 diabetic cohort; the present findings further elucidated that even a mild stage of DR is associated with a higher risk of both CHD and stroke.

Although a strong and consistent association between PDR and CVD has been reported, it is still controversial whether a milder stage of DR (i.e., nonproliferative DR) is associated with an increased risk of CVD. Mild nonproliferative DR was not associated with an increased risk of stroke in persons with older-onset diabetes in 16 years of follow-up,[23] and any level of DR was not associated with stroke in persons with type 1 diabetes in the WHO Multinational Study of Vascular Disease in Diabetes.[5] An association between nonproliferative DR and risk of CHD was not significant in a Finnish study.[30] This study found a significant increasing trend in risk of CVD by increasing severity of DR. The observed strength of association between the presence of relatively mild stage DR and CVD seems to be in concordance with previous epidemiologic studies. In the present study, risk of stroke and CHD were approximately 1.7 times higher in persons with mild to moderate nonproliferative DR than in those without DR, which was slightly weaker than that found with PDR. This supports indirectly that there is an increasing association between severity of DR and higher risk of CVD even at a milder stage of DR. There have not been many studies reporting detailed associations of DR level and risk of CVD. Klein et al[12] reported an increasing association between severity of DR and CVD in people with type 1 diabetes. They categorized DR severity into 4 groups of no DR, early nonproliferative DR, moderate to severe nonproliferative DR, and PDR, and risk of mortality including any heart disease outcome was increased by 30% for each higher severity of DR. In the diabetic participants of the ARIC study, which is assumed to be mainly type 2 diabetic patients, there were no increasing associations observed between retinopathy grade and risk of ischemic stroke.[7]

This study found that the presence of retinal hemorrhages (dot or blot) or retinal microaneurysms was associated with a 60% to 80% increased risk of CHD and any CVD. Retinal hemorrhages and microaneurysms are well recognized as early signs of DR. In the international severity scale for DR, presence of dot hemorrhages per se are categorized into mild nonproliferative DR, that is, the mildest stage in the classification.[15] In the ARIC study,[7] the presence of microaneurysms was associated significantly with incident ischemic stroke after adjusting for cardiovascular risks, whereas the presence of retinal hemorrhages did not increase the risk. This study also found an association between cotton-wool spots and increased risk of stroke. Pathologically, cotton-wool spots in the retina constitute a focal retinal capillary obstruction[31]; ischemic change in the retina observed as cotton-wool spots may reflect similar pathologic changes in the cerebral microcirculation related to stroke. Retinal and cerebral vasculatures share similarities in embryologic, anatomic, and physiologic characteristics[32,33]; retinal microvasculature may provide a window to observe vascular health directly in vivo.[32,33] Patton et al[33] pointed out that constituents of both retinal and cerebral microvasculatures are common (i.e., endothelial cells surrounded by pericytes, supported by basement membranes, and further surrounded by glial cells), and they have so-called barrier endothelia for mechanical and metabolic activities. An autoregulated mechanism to maintain constant blood flow is another common property of both retinal and cerebral circulation.[33] Assessing cerebral vasculature, especially for microcirculation, remains challenging; we speculate that simple direct visualization of retinal microvasculature may provide information of concurrent pathologic features in the cerebral vasculature. Supporting this finding and this concept, the ARIC study reported that the presence of cotton-wool spots was associated with a 2-fold risk of having subclinical cerebral infarction detected by magnetic resonance imaging scans,[34] and the presence of cotton-wool spots was associated with a 3-fold risk of incident stroke in a nondiabetic population.[35] In a diabetic population in the ARIC study, the association between cotton-wool spots and ischemic stroke was attenuated to nonsignificance after adjusting for other cardiovascular risk factors.[7] This is partially in keeping with the present findings, which suggest that potential variation in the association may exist for specific subtypes of stroke (i.e., ischemic infarction or hemorrhagic stroke).

Significant associations were found between mild stage DR and CVD independent of cardiovascular risk factors. Furthermore, whether integrating DR status into the CVD risk prediction models contributes to better prediction was examined. Although changes in the AUC were not statistically significant when adding DR lesions onto UKPDS proposed cardiovascular risk factors for CHD and stroke, there were moderate improvements. The most beneficial effect in reclassifying cases and noncases by adding DR information was observed for the stroke prediction model where the model with DR reclassified 12% of stroke cases and 1% of noncases correctly compared with the model without DR, with minimal tradeoffs of reclassifying 1% of cases and 4% of noncases incorrectly. The clinical relevance of incorporating DR assessment in a risk prediction model for CHD or stroke in addition to traditional cardiovascular markers may need further investigation. Although there are many attempts to refine CVD risk prediction using newer risk markers, such as high-sensitivity C-reactive protein or a combination of multiple markers, there are modest improvements in their performance on CVD risk prediction and they are now established as robust markers.[36–40] Kim et al[36] reported that when 18 new potential biomarkers were added to a traditional risk factor model, there was significant improvement in the AUC (+0.02) and net reclassification of 6.45%. Observed in this study was a +0.037 improvement in AUC for stroke and a +13% net reclassification when adding DR information to traditional risk factors of UKPDS risk engine; the usefulness of DR assessment as a biomarker of stroke prediction warrants further study to explore its potential. The strength of using DR assessment as a biomarker of CVD may include its long-term stability. Based on a 4-year observation in the older-onset diabetic patients in the Wisconsin Epidemiological Study of Diabetic Retinopathy, 15% to 19% of eyes with DR improved more than 2 step in the ETDRS severity scale.[41] However, no improvement was observed in persons with a level of DR of less than 21/21, which corresponds to mild nonproliferative DR.[41] This is keeping with the clinical impression that it is not likely to see complete natural resolution as soon as diabetic patients demonstrate any level of DR. When con-

sidering the presence of DR as a biomarker to predict CVD, this characteristic is beneficial because it is stable over time. Also, given that assessment of DR already is performed routinely by ophthalmologists, sharing this information and using it proactively in CVD risk assessment will benefit both clinicians and patients for achieving better prediction of CVD with minimum additional effort and cost; additional cost could be one of the concerns for adopting a new biomarker for CVD in clinical practice.[40]

The implications of these study findings in daily clinical practice should be emphasized. The data suggest that even with the most mild form of DR, patients already are at approximately a 70% higher risk of CVD developing, independent of cardiovascular risks. Furthermore, when ophthalmologist see progression of DR, this suggests increasing risk of CVD at the same time. Ophthalmologists need to inform the patients and physicians or diabetologists who are managing diabetes to optimize modifiable cardiovascular risk factors immediately.

Limitations of this study should be mentioned. First, DR was not confirmed by centralized grading of the fundus photographs. Although the agreement between ophthalmologists in each site was confirmed, it was moderate and misclassification was possible. This may result in overlooking the pathologic features of DR and underestimating the number of patients with DR. Misclassification for milder stage DR also is possible. These in turn may result underestimation of the association between DR and CVD. Second, persons with more severe stages of DR were not included because the study aimed to examine the incidence and progression from mild to severe stages of DR as the primary outcomes. External validity of this study also may be compromised because the participants of this study were a relatively well-managed type 2 diabetic cohort. The association between DR and increased risk of CVD in an Asian population should be confirmed further in a larger longitudinal study with a broader spectrum of potential confounding factors.

In conclusion, this study found that risk of CVD is increased even with a mild stage DR in type 2 diabetic Japanese persons over the 8-year follow-up of the JDCS. Further studies are required to validate the role of DR assessment for CVD risk stratification in clinical contexts.

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