Table 3 | Intake of selected food groups per day

	Men (n = 807)		Women (n = 709)		Age <60 years (n = 755)		Age ≥60 years (n = 761)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Grains (g)	207	58	173	40	194	54	189	52
Potato/aroid (g)	50	40	58	50	50	41	57	49
Soybeans/soy products (g)	68	49	75	54	71	51	72	52
Fruits (g)	121	101	148	108	126	107	140	103
Green-yellow vegetables (g)	130	69	147	66	136	67	140	68
Other vegetables (g)	174	103	200	99	184	100	188	104
Meat (g)	52	37	47	39	54	40	46	36
Fish (g)	103	61	97	59	101	61	100	60
Eggs (g)	30	18	28	16	29	16	29	17
Milk/dairy products (g)	165	109	177	94	168	108	173	97
Sweets/snacks (g)	16	20	20	21	18	21	17	20
Oil (g)	17	9	17	9	18	9	16	8
Alcoholic beverages (g)	155	195	14	48	99	180	80	142
Other beverages (g)	44	85	28	67	41	84	33	70

	Diabetes duration <10 years (n = 737)		Diabetes duration ≥10 years (n = 779)		Total (n = 1,516)	
	Mean	SD	Mean	SD	Mean	SD
Grains (g)	191	54	192	53	191	53
Potato/aroid (g)	56	45	51	45	54	45
Soybeans/soy products (g)	73	55	69	48	71	52
Fruits (g)	138	116	129	93	133	105
Green-yellow vegetables (g)	141	67	135	69	138	68
Other vegetables (g)	191	100	181	104	186	102
Meat (g)	51	39	48	37	50	38
Fish (g)	102	62	98	58	100	60
Eggs (g)	29	17	29	16	29	17
Milk/dairy products (g)	169	107	172	98	170	103
Sweets/snacks (g)	19	22	17	19	18	21
Oil (g)	18	9	16	9	17	9

Table 3 | (Continued)

	Diabetes duration <10 years (n = 737)		Diabetes duration ≥10 years (n = 779)		Total (n = 1,516)	
	Mean	SD	Mean	SD	Mean	SD
Alcoholic beverages (g)	91	174	86	147	89	162
Other beverages (g)	38	81	35	73	37	77

HbA1c, glycated hemoglobin; SD, standard deviation.

Table 4 | Summary of literature on dietary composition of diabetic patients including the current Japanese Diabetes Complications Study results

Study name or author	Method for measurement of dietary intake	Years carried out	Study population	Type of diabetes	No. participants (No. men)	Mean age (years)†	Energy intake (kcal)†	Carbohydrate intake (% energy)†	Fat intake (% energy)†	BMI†
Present study (JDCS)	FFQg	1996	Japanese	Type 2 diabetes	1,516 (805)	M: 58.4 W: 59.0	M: 1,819 W: 1,643	M: 53.0 W: 54.2	M: 26.7 W: 28.7	M: 22.7 W: 23.2
EURODIAB IDDM Complications Study Group[6]	3-day record	NA	European	IDDM	2,868 (1458)	33	M: 2,202 W: 1,604	M: 43.1 W: 41.9	M: 37.9 W: 37.9	M: 26 W: 28
	7-day food diaries	1993–1994	Spanish	Type 1 diabetes	144 (70)	M: 25.0 W: 27.1	M: 2,217 W: 1,623	M: 39.5 W: 40.0	M: 41.5 W: 40.5	M: 22.4 W: 23.2
DNCT[3]				Type 2 diabetes	193 (81)	M: 62.2 W: 62.5	M: 1,788 W: 1453	M: 39.0 W: 38.0	M: 38.5 W: 36.0	M: 25.8 W: 28.5
Strong Heart Study (SHS)[5]	24-h dietary recall	1997–1999	American Indians	Diabetes	1,008 (316)	M: 63.5 W: 63.5	M: 1,595 W: 1,422	M: 48.7 W: 48.7	M: 35.3 W: 35.9	M: 30.6 W: 32.8
NHANES[5]	24-h dietary recall	1999–2000	General US population	Diabetes	373 (190)	M: 64.9 W: 65.3	M: 1,852 W: 1,384	M: 48.4 W: 49.8	M: 34.7 W: 33.8	M: 30.5 W: 32.8
Diabetic Educational Eating Plan study[4]	7-day dietary recall	2005–2006	Clinical trial participants in USA White 85%, Black 5%, Asian 5%, other 5%	Type 2 diabetes	40 (19)	53.5	1,778	36.7	44.6	35.8 <25 5.0% 25–30 17.5% ≥30 77.5%
Lee *et al.*[20]	24-h dietary recall	2003–2004	Korean	Type 2 diabetes	154 (78)	61	M: 1,788 W: 1,546	M: 66.7‡ W: 68.4‡	M: 16.3‡ W: 16.2‡	M: NA W: NA
Kamada *et al.*[2]	FFQg	2001	Japan	Type 2 diabetes	912 (417)	M: 71.4 W: 72.3	M: 1,802 W: 1,661	M: 59.5 W: 58.6	M: 25.4 W: 25.8	M: 23.5 W: 24.0
Nthangeni *et al.*[21]	24-h dietary recall	1998	South African	Type 2 diabetes	290 (133)	<40§	M: 1,971¶ W: 1,712¶	M: 66.7 W: 65.8	M: 13.4 W: 14.4	M: ≥30 15.8% W: ≥30 40.8%

BMI, body mass index; DNCT, Diabetes Nutrition and Complications Trial; EURODIAB IDDM, European Diabetes Centers Study of Complications in Patients with Insulin-Dependent Diabetes Mellitus; IDDM, insulin-dependent diabetes mellitus; JDCS, Japan Diabetes Complications Study; M, men; NA, not available; NHANES, National Health and Nutrition Examination Survey; SHS, Strong Heart Study; W, women. †Maximum value and minimum value are shown if mean value was not available. ‡Estimated from mean value. §Age range was described because mean age was not reported. ¶1 kcal = 4.184 kJ.

厚生労働科学研究費補助金（循環器疾患等生活習慣病対策総合研究事業）
日本人2型糖尿病患者における生活習慣介入の長期予後効果
並びに死亡率とその危険因子に関する前向き研究
(Japan Diabetes Complications Study; JDCS)
平成２５年度　分担研究報告書

糖尿病の大規模臨床研究への期待と展望

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研究要旨　糖尿病の大規模臨床研究への期待と展望を述べた

本研究を含む２型糖尿病対象の大規模臨床研究によって以下の点が明らかにされた：細小血管症予防における血糖と血圧低下治療の有効性、大血管症の予防における、脂質・血圧・血糖低下治療の有効性。血糖･脂質・血圧の全てを管理する集学的治療の有用性、などである。一方、HbA1c、LDL-C（またはnon-HDL-C)、外来血圧などの指標について一定の目標値を目指す方法(Treat to target)に関する最近の検証結果によると、これまで正常と考えられてきたHbA1cや外来血圧を目標値に据えると、却って死亡率が増加し、患者の利益にならない懸念が浮上してきた。治療目標は必ずしもHbA1cの正常化にあるのではなく、重症低血糖を避け、血糖や血圧の変動性も考慮にいれるべきという考え方に変わってきた。日本人でも同様であろうか？例えば、現在進行中のJDOIT3では、強化治療群の目標値は正常値近くに設定されている。従って、そのデータを利用すれば、上述の問題が日本人にも当てはまるか否かという命題の検証が可能であろう。

また、近年の血糖低下療法は変革期にあり、インクレチン関連薬(DPP4阻害薬やGLP1受容体作動薬)やSGLT2阻害薬が従来の薬物療法に新たに追加された。このような状況は、選択肢の増加として歓迎すべき側面を有する反面、以下のようは問題点も指摘されている。例えば、血糖低下薬の効果は多くの場合一時的であり、程度の差はあれエスケープ現象を示す。従って、実臨床では、エスケープ現象を追いかけて、複数の血糖低下薬が併用されることが多い。しかし、多剤併用という治療のスタイルが糖尿病の進行や合併症を真に阻止しているかという命題や、医療経済に与えうる影響については十分検証されているとはいえない。更に、血糖値だけが２型糖尿病の真の進行度を反映していないという問題もある。従って、合併症はもちろん、２型糖尿病の病期を真に反映する臨床指標もエンドポイントに設定する必要があろう。その上で、多剤併用療法も含めた薬物療法の有効性と安全性の検証は、次に解決すべき大きな課題であろう。

厚生労働科学研究費補助金(循環器疾患等生活習慣病対策総合研究事業)

日本人２型糖尿病患者における生活習慣介入の長期予後効果並びに死亡率とその危険因子に関する前向き研究

(Japan Diabetes Complications Study; JDCS)

平成２５年度　分担研究報告書

本研究を含む糖尿病の大規模臨床研究への期待と提案

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研究要旨

糖尿病における血管合併症の予防、進展抑制を目的としたJDCS研究を含む糖尿病の大規模臨床研究の成果を踏まえ、従来の危険因子以外にライフスタイルの運動、食事、心理が糖尿病合併症の危険因子として重要である。今後、そうした糖尿病合併症のリスクエンジンが作成することが必要であると思われる。

A. 目的と研究方法：JDCS研究は、我が国の糖尿病患者における血管合併症の危険因子について検討してきた。そこで、JDCS研究のみならず、高齢糖尿病患者のJ-EDIT研究の成果も加えて、血管合併症の危険因子の特徴を見出し、糖尿病の大規模臨床研究への期待と提案について考察を加えてみた。

B. 研究結果と考察：JDCS研究では身体活動量の低下が、他の従来の危険因子を調整しても脳卒中や死亡のリスクであった。また、果物の摂取が従来の危険因子を補正しても網膜症のリスクを減少させた。J-EDIT研究でも同様に、身体活動量の低下は脳卒中発症と関連した。また、うつ症状が多いことも脳卒中の発症と関連した。JDCS研究では電話等の介入群は、対照群と比べて、従来の危険因子とは無関係に脳卒中の発症頻度が減少した。したがって、血糖、血圧、脂質など以外に、ライフスタイルである運動、栄養、心理の状態が糖尿病合併症の発症に直接関与することが考えられる。

C. 結論：こうした大規模臨床試験の成果を踏まえ、糖尿病患者が注意すべきライフスタイルを組み合わせた糖尿病合併症のリスクエンジンが作成されることが望まれる。

D. 実用新案登録： なし

Diabetic Retinopathy and Microalbuminuria Can Predict Macroalbuminuria and Renal Function Decline in Japanese Type 2 Diabetic Patients

Japan Diabetes Complications Study

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OBJECTIVE—To examine the interactive relationship between diabetic retinopathy (DR) and diabetic nephropathy (DN) in type 2 diabetic patients and to elucidate the role of DR and microalbuminuria on the onset of macroalbuminuria and renal function decline.

RESEARCH DESIGN AND METHODS—We explored the effects of DR and microalbuminuria on the progression of DN from normoalbuminuria and low microalbuminuria (<150 mg/gCr) to macroalbuminuria or renal function decline in the Japan Diabetes Complications Study (JDCS), which is a nationwide randomized controlled study of type 2 diabetic patients focusing on lifestyle modification. Patients were divided into four groups according to presence or absence of DR and MA: normoalbuminuria without DR [NA(DR−)] (n = 773), normoalbuminuria with DR [NA(DR+)] (n = 279), microalbuminuria without DR [MA(DR−)] (n = 277), and microalbuminuria with DR [MA(DR+)] (n = 146). Basal urinary albumin-to-creatinine ratio and DR status were determined at baseline and followed for a median of 8.0 years.

RESULTS—Annual incidence rates of macroalbuminuria were 1.6/1,000 person-years (9 incidences), 3.9/1,000 person-years (8 incidences), 18.4/1,000 person-years (34 incidences), and 22.1/1,000 person-years (22 incidences) in the four groups, respectively. Multivariate-adjusted hazard ratios of the progression to macroalbuminuria were 2.48 (95% CI 0.94–6.50; P = 0.07), 10.40 (4.91–22.03; $P < 0.01$), and 11.55 (5.24–25.45; $P < 0.01$) in NA(DR+), MA(DR−), and MA(DR+), respectively, in comparison with NA(DR−). Decline in estimated glomerular filtration rate (GFR) per year was two to three times faster in MA(DR+) (−1.92 mL/min/1.73 m^2/year) than in the other groups.

CONCLUSIONS—In normo- and low microalbuminuric Japanese type 2 diabetic patients, presence of microalbuminuria at baseline was associated with higher risk of macroalbuminuria in 8 years. Patients with microalbuminuria and DR showed the fastest GFR decline. Albuminuria and DR should be considered as risk factors of renal prognosis in type 2 diabetic patients. An open sharing of information will benefit both ophthalmologists and diabetologists.

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Diabetic retinopathy (DR) and nephropathy (DN) are two major chronic microvascular complications in long-standing type 1 and type 2 diabetic patients. However, it is still unclear whether these 2 complications are related to or affect each other or whether both of them progress simultaneously after their onset, although many epidemiological studies have shown the coexistence of DR and DN (1,2). In fact, we sometimes see proteinuric diabetic patients without DR or normoalbuminuric patients with proliferative DR, which is the most advanced stage of DR. For example, it was shown that only 36% had no DR, while 53% had nonproliferative, 9% moderate to severe, and 2% severe DR in 285 normoalbuminuric Caucasian type 1 diabetic patients (3). In addition, there was marked discordance between DR and DN, especially in normoalbuminuria or low-level microalbuminuria, while advanced renal histological severity has been related to advanced DR severity in Caucasian type 1 diabetic patients (4). On the other hand, diabetic patients treated by diabetologists sometime miss their visits to ophthalmologists; therefore, the relationships or detailed clinical courses of DR and DN can hardly be analyzed in most clinical sites.

All over the world, DN is a major cause of end-stage renal disease, which

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requires renal replacement therapy such as hemodialysis or renal transplantation (5,6). In Japan, the number of patients requiring renal replacement therapy has increased threefold in the last 15 years. Therefore, it is absolutely necessary to stop the progression of DN and to find biomarkers or easily available factors that represent the exact clinical course or prognosis of DN. However, it is not exactly known what factors affect an increase of urinary albumin excretion (UAE) or glomerular filtration rate (GFR) decline, which are typical clinical changes in DN.

Microalbuminuria is well known as a risk factor resulting in macroalbuminuria in type 1 and type 2 diabetic patients (7–9). In addition, some Caucasian type 2 diabetic patients with microalbuminuria showed rapid decline of GFR, although it was unclear whether these patients had more frequent DR compared with the patients without rapid GFR decline (10). On the other hand, DR was shown to be a risk factor of microalbuminuria and macroalbuminuria (2,11). In addition, proliferative DR was shown to be a predictor of macroalbuminuria in Caucasian type 1 diabetic patients (13), but this association has not been investigated in Asian populations. Although DR and glomerulosclerosis seemed to be parallel to progress using the investigation of serial renal biopsy specimens (14) when the blood glucose control was fair to poor, detailed interaction between two complications are still obscure in a large number of patients. Whether DR can predict renal functional decline in type 1 and type 2 diabetic patients remains to be clarified.

The Japan Diabetes Complications Study (JDCS) is a nationwide randomized controlled study of type 2 diabetic patients focusing on lifestyle modification (15,16). We have reported the extremely low transition rate from normoalbuminuria and low microalbuminuria in this Japanese cohort (9), as well as incidence and progression rates of DR that were also lower than in Caucasian populations (15). In addition, we have also shown that the incidence and progression rate of DR were lower than those in Caucasian populations and that glycemic control, duration of diabetes, and systolic blood pressure (SBP) were related to DR in the JDCS cohort (17). Here, we elucidated the relationships between DN and DR, and the risk factors of the UAE increase and GFR decline according to the presence or absence of microalbuminuria or DR in the JDCS cohort.

RESEARCH DESIGN AND METHODS

This study is a part of the JDCS, a Japanese nationwide multicentered randomized trial (15). In 1996, 2,205 patients aged 40–70 years with previously diagnosed type 2 diabetes and HbA_{1C} levels of >6.5% were recruited and registered from 59 hospitals specializing in diabetes care. The protocol for the study, which is in accordance with the Declaration of Helsinki and the Ethical Guidelines for Clinical/Epidemiological Studies of the Japanese Ministry of Health, Labor and Welfare, received ethics approval from the institutional review boards of all the participating institutes. Written informed consent was obtained from all patients enrolled. The inclusion criteria for participating patients have previously been described (15). Those who had impaired glucose tolerance and major ocular disease including glaucoma, dense cataract, or history of cataract surgery were excluded. A final total of 2,033 patients aged 58.5 ± 6.9 (mean ± SD) years were included in the study, and their known diabetes duration was 10.9 ± 7.2 years.

The protocol originally specified that patients with nondiabetic nephropathy, macroalbuminuria, serum creatinine levels >120 μmol/L, and mean values of two spot urine examinations for an albumin excretion rate of >150 mg/g creatinine were excluded in the analysis of nephropathy, making up the analysis population of 1,558 patients (9). We excluded the patients with high microalbuminuria (150–300 mg/gCr) because the INNOVATION (Incipient to Overt: Angiotensin II Receptor Blocker, Telmisartan, Investigation on Type 2 Diabetic Nephropathy) trial showed a higher transition rate from high microalbuminuria to macroalbuminuria (18). After exclusion of 83 patients without DR assessment, the remaining 1,475 patients were divided into four groups according to the absence or presence of DR and microalbuminuria as follows: normoalbuminuria without DR [NA(DR−)] (n = 773), normoalbuminuria with DR [NA(DR+)] (n = 279), microalbuminuria without DR [MA(DR−)] (n = 277), and microalbuminuria with DR [MA(DR+)] (n = 146).

Assessment of DR

The presence and severity of DR were determined annually by qualified ophthalmologists at each institute by mydriatic indirect ophthalmoscopic examination and slit lamp biomicroscopic fundus examination using precorneal lens with the international DR and diabetic macular edema disease scales including minor modifications (17,19). To validate the consistency of staging between study sites, we cross-examined fundus images and evaluated the agreement in staging between local ophthalmologists and retinal specialists (17). Severity of DR was categorized following the international clinical diabetic retinopathy severity scales into five categories as "no retinopathy" (equivalent to the Early Treatment of Diabetic Retinopathy Study [ETDRS] scale level 10), "mild nonproliferative DR" (stage 1; equivalent to ETDRS level 20), "moderate nonproliferative DR" (stage 2; equivalent to ETDRS levels 35, 43, and 47), "severe nonproliferative DR" (stage 3; equivalent to ETDRS levels 53A–53E), and "proliferative DR" (stage 4; equivalent to ETDRS levels ≥61) (19). History of ocular surgery (e.g., cataract, glaucoma, and vitreoretinal surgery) was also surveyed.

Measures of kidney function

We followed up these groups for 8 years and measured their body weight and blood pressure at least twice a year. HbA_{1c}, fasting plasma glucose, serum lipids, and serum creatinine levels were also determined twice a year. Spot urinary albumin-to-creatinine ratio (UACR) was also determined at least twice a year using the turbidmetric immunoassay to measure the urinary albumin concentration. We defined normoalbuminuria as a UACR <30 mg/gCr and low microalbuminuria as a UACR of 30–150 mg/gCr. Estimated GFR (eGFR) was calculated using serum creatinine levels and ages according to the Modification of Diet in Renal Disease formula modified for the Japanese population (20).

Statistical analysis

The annual increase rate of UACR and decline rate of eGFR in each group was determined by linear mixed models. The transition from normo- or low microalbuminuria to macroalbuminuria (≥300 mg/gCr) was determined in two consecutive urine samples. Transition to macroalbuminuria was summarized by the annual transition rate to macroalbuminuria, and the remission proportion was defined by patients whose mean value of UACR at the final two visits was <30 mg/gCr. Hazard ratios of the NA(DR+), MA(DR−), and MA(DR+) groups compared with the NA(DR−) group as a reference adjusted for age, sex, HbA_{1c}, known duration of diabetes, SBP, and current smoking were estimated by Cox regression. All

P values are two sided, and the significance level is 0.05. All statistical analyses and data management were conducted at a central data center using SAS version 9.2 (SAS Institute, Cary, NC).

RESULTS

Baseline clinical characteristics between four diabetic groups

LDL cholesterol, eGFR, and treatment of dyslipidemia did not differ between the four groups. Age, sex, HbA_{1c}, known duration of diabetes, BMI, blood pressure, HDL cholesterol, triglyceride, percent of current smokers, or treatment of diabetes and hypertension were different among the four groups at the baseline. UACR did not show any difference between NA(DR−) and NA(DR+) at normoalbuminuric levels or between MA(DR−) and MA(DR+) at microalbuminuric levels. The majority of the DR-positive patients had mild nonproliferative DR (stage 1) (Table 1).

Cox regression analysis for baseline albuminuria/retinopathy and incidence of macroalbuminuria

During the follow-up of a median of 8.0 years, a total of 73 progressions to macroalbuminuria were observed. The follow-up rate at 8 years was 78%. The numbers of death were 58 (3.9%) during the observation. Annual incidence rates of macroalbuminuria were 1.6/1,000 person-years (9 incidences), 3.9/1,000 person-years (8 incidences), 18.4/1,000 person-years (34 incidences), and 22.1/1,000 person-years (22 incidences) in the NA(DR−), NA(DR+), MA(DR−), and MA(DR+) groups, respectively. Table 2 shows multivariate-adjusted hazard ratios for the progression to macroalbuminuria. As shown, the hazard ratio of NA(DR+) compared with NA(DR−) was 2.48 (95% CI 0.94–6.50, $P = 0.07$). However, hazard ratios in MA(DR−) and MA(DR+) were 10.40 (4.91–22.03, $P < 0.01$), 11.55 (5.24–25.45, $P < 0.01$), and significantly higher than NA(DR−). These results also indicate that the hazard ratio for the direct comparisons between MA(DR+) and MA (DR−) is 0.90 (0.51–1.56, $P = 0.72$). Further, quantitatively similar trends are observed across severity of DR and microalbuminuria; hazard ratios of normoalbuminuria with stage 1, normoalbuminuria with stage 2–4, MA(DR−), microalbuminuria with stage 1 and microalbuminuria with stage 2–4 compared with NA(DR−) were 2.56 (0.95–6.90, $P = 0.06$), 2.38 (0.30–18.85, $P = 0.41$), 10.41 (4.92–22.01, $P < 0.01$), 10.06 (4.36–23.21, $P < 0.01$), and 21.30 (7.84–57.87, $P < 0.01$), respectively, using the same adjustment variables.

Clinical course of urinary albumin and eGFR among four groups >8 years old

Figure 1*A* and *B* show the UACR and eGFR over 8 years. The UACR had a trend toward an increase over time, and eGFR were decreased over time in all four groups. Annual increase rates of UACR in NA (DR+), MA(DR−) and MA(DR+) were 6.76 mg/gCr/year (95% CI 4.53–8.99, $P < 0.01$), 16.35 mg/gCr/year (13.97–18.74, $P < 0.01$), and 25.27 mg/gCr/year (22.13–28.41, $P < 0.01$), respectively, and they were significantly higher than in NA (DR−), which was 3.05 mg/gCr/year (1.72–4.39, $P < 0.01$). GFR decline per year in MA(DR+) was −1.92 mL/min/1.73 m^2/year (−2.28 to −1.55, $P < 0.01$) and was significantly faster than in NA (DR−), NA(DR+), and MA(DR−), which were −0.54 mL/min/1.73 m^2/year (−0.70 to −0.39, $P < 0.01$), −0.69 mL/min/1.73 m^2/year (−0.96 to −0.42, $P < 0.01$), and

Table 1—*Baseline characteristics of the 1,475 type 2 diabetic patients*

	NA(DR−)	NA(DR+)	MA(DR−)	MA(DR+)	ANOVA *P*
N	773	279	277	146	
Age (years)	57.9 ± 6.9	58.6 ± 6.9	59.2 ± 7.0	59.4 ± 6.5	<0.01
Mild nonproliferative DR (%)	0 (0)	239 (85.7)	0 (0)	117 (80.1)	ND
Moderate nonproliferative DR (%)	0 (0)	28 (10.0)	0 (0)	16 (11.0)	
Severe nonproliferative DR (%)	0 (0)	4 (1.4)	0 (0)	4 (2.7)	
Proliferative DR (%)	0 (0)	8 (2.9)	0 (0)	9 (6.2)	
Women, *n* (%)	348 (45.0)	149 (53.4)	134 (48.4)	69 (47.3)	<0.01
HbA_{1c} (%) (mmol/mol)	8.1 ± 1.3 (66 ± 14)	8.3 ± 1.2 (67 ± 13)	8.3 ± 1.3 (68 ± 15)	8.7 ± 1.4 (71 ± 15)	<0.01
Known diabetes duration (years)	9.7 ± 7.0	13.1 ± 7.4	9.5 ± 6.5	12.6 ± 6.3	<0.01
BMI (kg/m^2)	22.9 ± 3.0	22.6 ± 2.5	23.6 ± 3.1	23.9 ± 2.9	<0.01
SBP (mmHg)	129.3 ± 15.5	132.2 ± 15.6	136.5 ± 16.9	136.4 ± 16.9	<0.01
Diastolic BP (mmHg)	76.4 ± 9.9	75.9 ± 9.8	79.7 ± 10.0	77.5 ± 9.5	<0.01
LDL cholesterol (mg/dL)	122.2 ± 32.4	119.9 ± 31.7	125.8 ± 31.8	119.3 ± 33.9	0.12
HDL cholesterol (mg/dL)	54.4 ± 16.6	58.0 ± 18.0	53.1 ± 15.9	52.8 ± 14.3	<0.01
Triglyceride (mg/dL)	101.5 (74.0)	90.5 (60.0)	107.5 (85.0)	104.0 (78.0)	<0.01
Spot UACR (mg/gCr)	11.2 (0.05–30.0)	11.5 (0.01–29.9)	52.3 (30.0–148.9)	55.6 (30.0–147.4)	ND
eGFR (mL/min/1.73 m^2)	87.3 ± 28.7	86.0 ± 25.2	89.9 ± 33.5	87.5 ± 29.7	0.45
Treated by insulin (%)	108 (14.0)	87 (31.2)	33 (11.9)	38 (26.0)	<0.01
Treated by OHA without insulin (%)	504 (65.2)	195 (69.9)	170 (61.4)	107 (73.3)	0.04
Current smoker (%)	213 (27.6)	57 (20.4)	82 (29.6)	28 (19.2)	0.01
Treated by antihypertension agents	161 (20.8)	73 (26.2)	103 (37.2)	54 (37.0)	<0.01
Treated by lipid-lowering agents	179 (23.2)	76 (27.2)	71 (25.6)	37 (25.3)	0.55

Data are *n* (%), *n*, or means ± SD unless otherwise indicated. Triglyceride is expressed as median (interquartile range). UACR is expressed as median (range). ND, not done for the selection criteria; OHA, oral hypoglycemic agents.

Table 2—*Cox regression analysis for the incidence of macroalbuminuria by presence or absence of baseline albuminuria/retinopathy and other risk characteristics*

	Hazard ratio	95% CI	*P*
Normoalbuminuria			
Retinopathy absent	1	Ref.	—
Retinopathy present	2.48	0.94–6.50	0.07
Microalbuminuria			
Retinopathy absent	10.40	4.91–22.03	<0.01
Retinopathy present	11.55	5.24–25.45	<0.01
Age, +10 years	1.13	0.78–1.61	0.52
Sex, male/female	0.80	0.46–1.38	0.42
Known duration of diabetes, +10 years	1.10	0.76–1.60	0.61
HbA_{1c}, +1%	1.34	1.15–1.56	<0.01
SBP, +10 mmHg	1.10	0.96–1.27	0.17
Smoking status			
Past or never smoker	1	Ref.	—
Current smoker	1.90	1.12–3.25	0.02

−0.69 mL/min/1.73 m^2/year (−0.96 to −0.42, $P < 0.01$), respectively.

Course of UAE according to baseline diabetic retinopathy

As we found in the multivariate analysis in Table 2, patients with DR progressed from normoalbuminuria to high microalbuminuria (UACR; 150–300 mg/gCr) or macroalbuminuria (UACR >300 mg/gCr) more frequently than those without DR. However, remission rates of MA (DR−) and MA(DR+) groups from low microalbuminuria (UACR; 30 to 150 mg/gCr) at baseline to normoalbuminuria at the 8-year follow-up were 32.1 and 25.3%, respectively, showing no significant difference ($P = 0.18$) (Table 3).

CONCLUSIONS—In the previous report about DN in JDCS (9), we showed that the progression rate to macroalbuminuria from normoalbuminuria and low microalbuminuria was very low, and remission, i.e., normalization of low microalbuminuria to normoalbuminuria, was observed in 30.3% of patients. In the current study, we have shown that progression to macroalbuminuria was 2.48, 10.40, and 11.55 times faster than DR-free normoalbuminuria if patients had NA(DR+), MA(DR−), or MA(DR+), respectively. Of interest is the observation that the presence of both DR and microalbuminuria might be an important predictor of GFR decline in normoalbuminuric and low microalbuminuric type 2 diabetic patients during 8 years of follow-up.

Microalbuminuria, a phenotype of early DN, is one of the risk factors of macroalbuminuria (7,8). In addition, macroalbuminuria itself is known to be a risk factor resulting in renal function decline. In fact, a subset of microalbuminuric patients showed a rapid deterioration of renal function, which was evaluated with cystatin C–based eGFR (10). Another report (21) showed that normoalbuminuric type 2 diabetic patients had a decline in GFR similar to that in normal control subjects, while microalbuminuric patients showed more GFR loss for a 10-year follow-up. However, these reports (10,21) showed little information regarding DR. Microalbuminuria was indicated as a risk factor of DR in type 1 diabetic patients but not in type 2 diabetic patients (1). Thus, whether microalbuminuria itself or DR itself results in GFR decline must be examined to elucidate the exact and detailed clinical course of DN including both UAE and GFR changes (1).

Recently, DR has become known as a risk factor for all-cause mortality (22), cardiovascular event, and subclinical atherosclerosis (23) or cardiovascular disease (24). However, it is still obscure whether DR had some effects on UAE increase or GFR decline, especially in normoalbuminuric and low microalbuminuric diabetic patients. Thirty-eight Caucasian type 2 diabetic patients with macroalbuminuria showed higher rates of GFR decline during 6 years of observation when the patients had DR compared with the patients without DR (25). On the other hand, 25 Danish type 1 diabetic patients without macroalbuminuria revealed higher transition rates to macroalbuminuria when the patients had proliferative DR (13). In the current study, microalbuminuric patients with DR obviously revealed GFR decline, while normoalbuminuric patients with DR had a trend toward increase of UAE. In addition, hazard ratio was increased according to DR severity grade, especially in microalbuminuric patients. Therefore, we need to perform ophthalmological examination to detect DR carefully, especially in the patients with normo- or microalbuminuria, to identify persons at higher risk of developing macroalbuminuria. It has not been shown that DR itself is related to renal function decline, although some reports have shown that urinary abnormalities, microalbuminuria, or macroalbuminuria predicts DR (26), and microalbuminuria has been indicated to have a greater impact on predicting DR than GFR decline in type 2 diabetic patients (27).

There are few reports that both microalbuminuria and DR predict renal function loss. In Chinese populations, the reduction of eGFR of >50% or progression to eGFR <15 mL/min/1.73 m^2 or end-stage renal disease was predicted in the type 2 diabetic patients with microalbuminuria or DR compared with the patients with no complications (28). The risk of the renal outcome was obviously increased when both DR and microalbuminuria or macroalbuminuria were present (28). However, the report (28) did not show that the slope of GFR decline was related to the presence of microalbuminuria and DR. Therefore, the current study demonstrates for the first time that the rate of GFR decline was faster in patients with microalbuminuria and DR at the early stage of DN.

One of the reasons why UAE trended to be increased in normoalbuminuric patients with DR or GFR decreased in microalbuminuric patients with DR in the current study might be related to the severity of the renal histological changes including glomerular basement membrane (GBM) thickening and mesangial expansion. In fact, in normoalbuminuric type 1 diabetic patients, abnormal values of GBM thickness and mesangial expansion were more frequently seen in the patients with DR, and these histological changes aggravated according to DR grade (3). Another report (29) revealed that type 2 diabetic patients with macroalbuminuria showed more frequent Kimmelstiel-Wilson nodular lesions when the patients had proliferative DR.

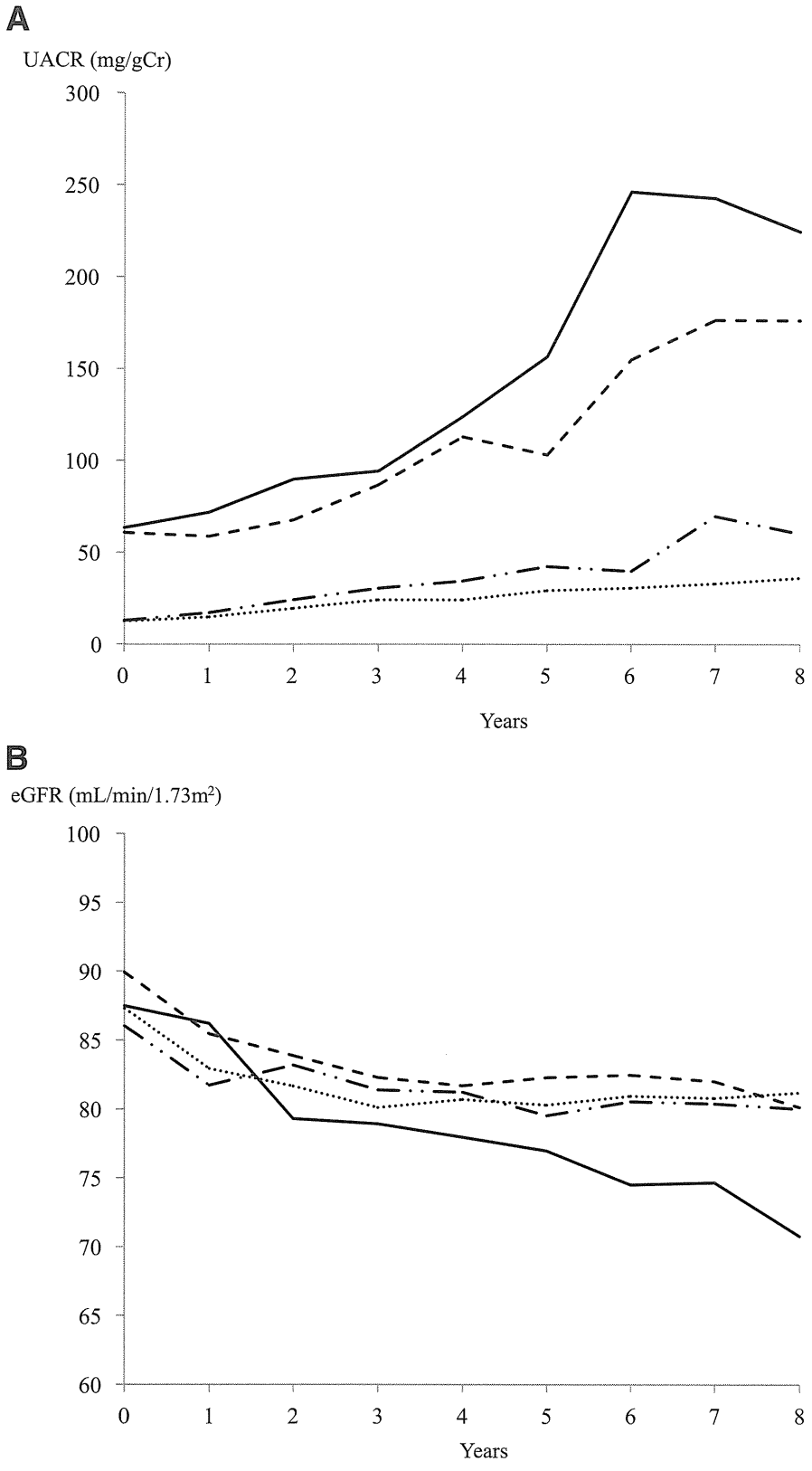

Figure 1—*The annual increase rate of UACR and decline rate of eGFR in each group. Dotted line, both normal; dash-dot line, retinopathy only; dashed line, albuminuria only; solid line, both abnormal.* A: *Two microalbuminuric groups showed a striking increase in UACR during the 8-year observation, although UACR in the two normoalbuminuric groups gradually increased more or less.* B: *The eGFR decline rate in the MA(DR+) group was significantly faster than that in the other three groups.*

The patients with nodular glomerulosclerosis frequently had an increase of serum creatinine within 5 years of follow-up (30). In addition, it was shown that renal histological changes were heterogeneous in microalbuminuric type 2 diabetic patients, and three histological categories of renal injury patterns were previously indicated (31). In the report (31), DR was present in all the patients with typical diabetic glomerular sclerosis. No proliferative DR was seen in the patients with a normal/near-normal pattern or atypical renal histological injury, while background DR was observed in 50 and 57% of patients, respectively. More recently, a link between quantitative assessment of the retinal vessel caliber size and change in glomerulopathy index including mesangial expansion and GBM thickening during 5 years follow-up was reported in normotensive normoalbuminuric Caucasian type 1 diabetic patients (32). Change in the retinal vessel caliber size has been speculated to be reflecting inflammation, endothelial dysfunction, and prevalence and incidence of DR (33). Therefore, DR might reflect renal histological severity as diabetic glomerulosclerosis regardless of albuminuria. In microalbuminuric Caucasian type 1 diabetic patients, the rate of annual GFR decline was related to renal histological change (34). In addition, in normo- and microalbuminuric Japanese type 2 diabetic patients, it was shown that UAE increased 5.6 years after the renal biopsy when renal histological changes, including mesangial expansion, were more severe (35). Thus, the patients with DR have more severe diabetic glomerular changes, which are followed by UAE increase or GFR decline compared with the patients without DR. Further examinations will be warranted to confirm the difference of histological changes among the four groups shown in the current study.

In the JDCS cohort, both blood pressure and glycemic control were risk factors of the occurrence of DR and the transition from normo- and low microalbuminuria to macroalbuminuria, whereas the duration of diabetes was a predictor for DR and smoking was a predictor for DN (9,17). In the previous study (9), progression to macroalbuminuria was independently associated with higher baseline HbA_{1c} and SBP levels in addition to an elevated baseline UACR; and smoking was a significant predictor of macroalbuminuria as well. These factors were also significant predictors of

Table 3—*Course of UAE according to baseline diabetic retinopathy*

	Final ACR (mg/gCr)							
	<30		30–150		150–300		≥300	
	n	%	*n*	%	*n*	%	*n*	%
No retinopathy								
Basal ACR <30 mg/gCr (*n* = 773)	593	76.7	158	20.4	13	1.7	9	1.2
Basal ACR 30–150 mg/gCr (*n* = 277)	89	32.1	124	44.8	30	10.8	34	12.3
Retinopathy								
Basal ACR <30 mg/gCr (*n* = 279)	188	67.4	69	24.7	14	5.0	8	2.9
Basal ACR 30–150 mg/gCr (*n* = 146)	37	25.3	64	43.8	23	15.8	22	15.1

ACR, albumin-to-creatinine ratio.

macroalbuminuria in the current study. Therefore, achievement of good glycemic and blood pressure control and smoking cessation education would be valuable to avoid GFR decline in type 2 diabetic patients, which will be examined in larger populations.

Our study has certain limitations. The first is that death before the onset of macroalbuminuria is a competing risk that potentially influences the association between macroalbuminuria and its risk factors. We handled such patients as censored because the mortality in this study was low (only 58 deaths [3.9%]) and seemed not to have much effect on the results. The second is that the prognosis of DR has not been examined yet. It is very important to clarify whether the presence of baseline microalbuminuria affects the progression of DR. Therefore, further study is warranted to analyze the prognosis of DR using the same cohort in the future. The final one is that the current study was established when angiotensin II receptor blockers (ARBs) were not widely used in our country, unfortunately. Since ARBs became available in 1998 in Japan, the number of renin-angiotensin system (RAS) inhibitor usage was small—12.3% at baseline—and was increased gradually to 28.4% at 8 years' follow-up based on each physician's decision—not on the protocol (9). It is well known that RAS inhibitors including ACE inhibitors and ARBs remit microalbuminuria (36) or retard the onset of microalbuminuria (37). It is important to examine the detailed course of albuminuria or GFR prospectively, focusing on the effects of RAS inhibitors in a Japanese cohort in the future.

In conclusion, the presence of microalbuminuria and/or DR profoundly affects renal function in type 2 diabetic patients. Therefore, diabetologists and ophthalmologists should share their acquired information regarding DN and DR, even if it is at milder stages.

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T.M. researched data, contributed to the discussion, and wrote the manuscript. S.T. analyzed data. R.K. contributed to the discussion and reviewed and edited the manuscript. Y.O. analyzed data. Y.A. and N.Y. contributed to discussion. H.S. contributed to discussion and reviewed and edited the manuscript. H.Y. contributed to discussion. S.K. contributed to the discussion and reviewed and edited the manuscript. 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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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. Increasing DR severity is associated with an increased risk of vision loss and risk of vision-threatening proliferative disease over time. 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 and coronary heart disease (CHD). Kramer et al 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. Sasaki et al 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, 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.

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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. 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. 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 ( ). 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 (; 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). 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. 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. 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.

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. 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. 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. 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 ( ). 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 ( ). 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 ( ). 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;). 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 ($P<0.01$;). 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 ( ).

With the model estimating risk of CHD based on traditional cardiovascular risks factors proposed by the UKPDS, the AUC analysis improved from 0.682 in the model without DR (95% CI, 0.626–0.737; shown with light blue, A) to 0.697 in the model with DR (95% CI, 0.641–0.752; shown with dark blue, A). This difference did not reach statistical significance ($P = 0.22$). A 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.

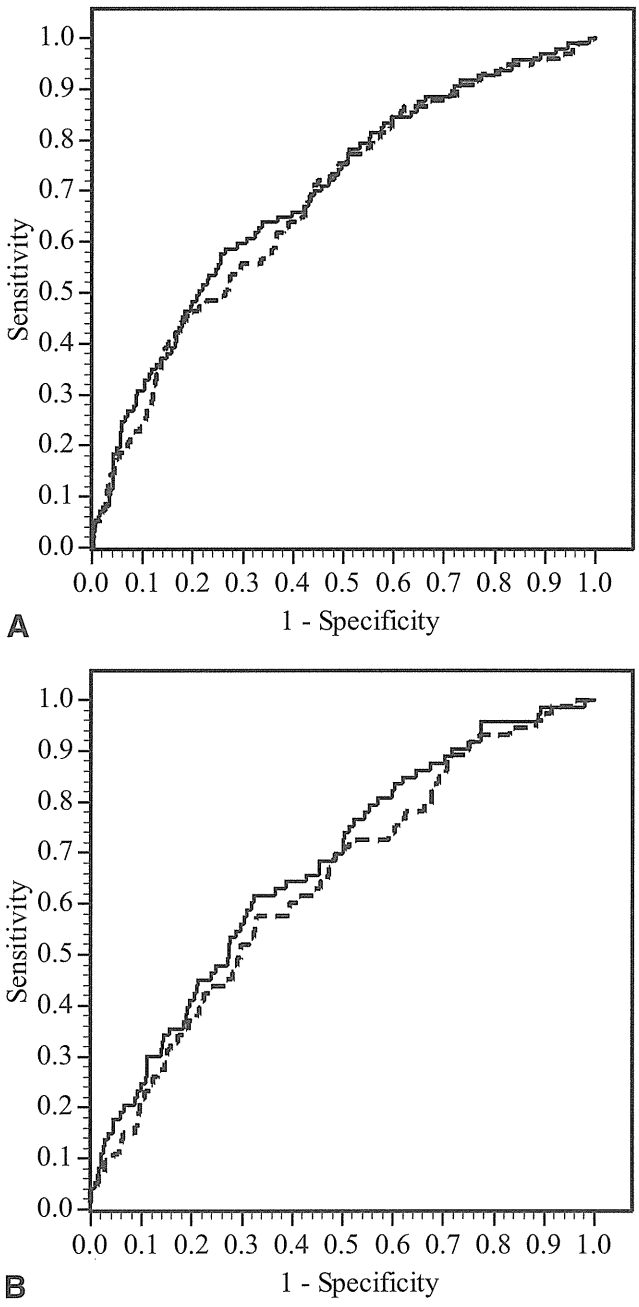

Figure 1. **A**, Graph showing a comparison of the receiver operating curves for coronary heart disease based on the United Kingdom Prospective Diabetes Study (UKPDS) risk factors with (solid line) or without (dashed line) diabetic retinopathy. **B**, Graph showing a comparison of receiver operating 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, B) to 0.677 (95% CI, 0.615–0.739; shown with light blue, B) by adding DR information; again, this difference was not statistically significant ($P = 0.12$). As shown in B, 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.

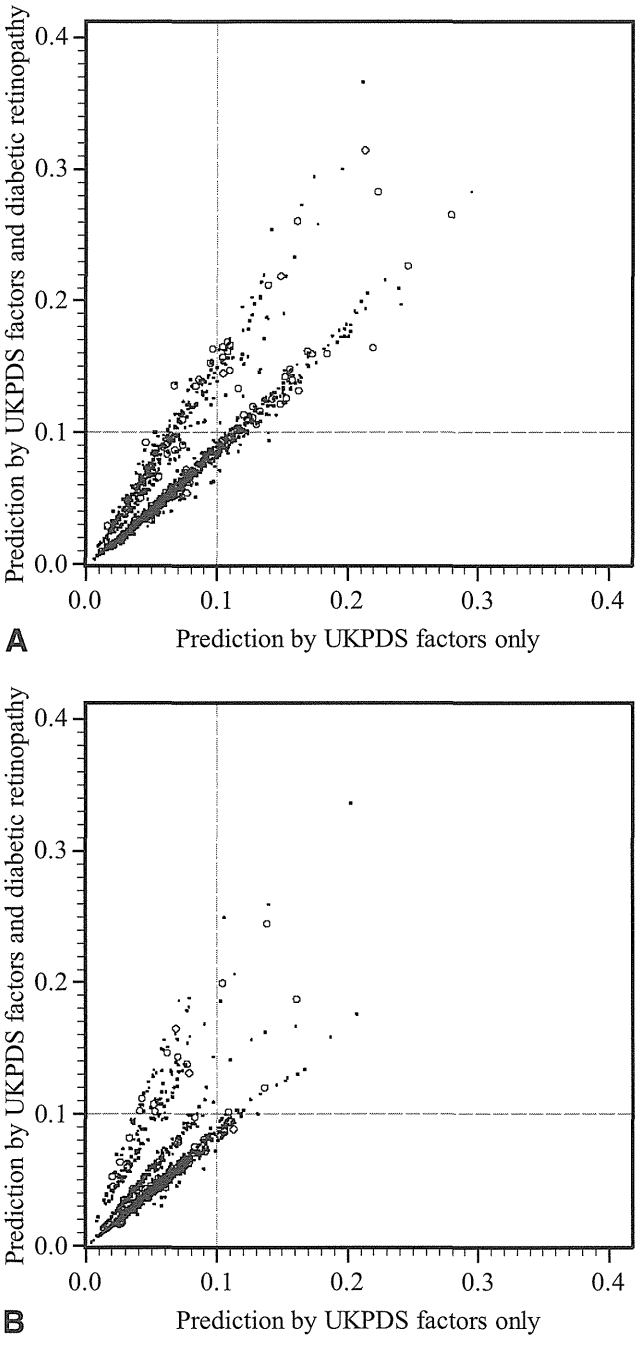

Figure 2. **A**, Graph showing the risk of coronary heart disease plotted for predicted risk by United Kingdom Prospective Diabetes Study (UKPDS) models with diabetic retinopathy against predicted risk by the UKPDS model without diabetic retinopathy. Reclassification of coronary heart disease is shown 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. 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. 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. Severity of DR also was associated with risk of stroke in persons with type 1 diabetes. 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. 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.

However, there has been limited knowledge from Asian populations. This is important because there exist differences in the epidemiologic and risk associations of CVD between a white population and an Asian Japanese population. For example, the incidence of stroke is much higher in Japanese persons than American Japanese persons in Hawaii. 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). 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, whereas lower high-density lipoprotein cholesterol was considered to be the second most important risk factor in the UKPDS. 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). 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 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, 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. An association between nonproliferative DR and risk of CHD was not significant in a Finnish study. 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 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.

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. In the ARIC study, 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 ; 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 ; retinal microvasculature may provide a window to observe vascular health directly in vivo. Patton et al 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. 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, and the presence of cotton-wool spots was associated with a 3-fold risk of incident stroke in a nondiabetic population. 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. 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. Kim et al 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. However, no improvement was observed in persons with a level of DR of less than 21/21, which corresponds to mild nonproliferative DR. 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.

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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