Diabetic Retinopathy Is Associated With Mortality and Cardiovascular Disease Incidence

The EURODIAB Prospective Complications Study

MANON V. VAN HECKE, MD[1,2]
JACQUELINE M. DEKKER, PHD[2]
COEN D.A. STEHOUWER, MD, PHD[2,3]
BETTINE C.P. POLAK, MD, PHD[1,2]
JOHN H. FULLER, FRCP[4]
ANNE KATRIN SJOLIE, DSCI[5]
ATHANASIOS KOFINIS, MD[6]
RAOUL ROTTIERS, MD[7]
MASSIMO PORTA, MD, PHD[8]
NISH CHATURVEDI, MRCP[9]

OBJECTIVE — To study the relationship of nonproliferative and proliferative retinopathy with all-cause mortality and cardiovascular disease (CVD) incidence in type 1 diabetic patients and, additionally, the role of cardiovascular risk factors in these associations.

RESEARCH DESIGN AND METHODS — This prospective study included 2,237 type 1 diabetic patients from 31 centers in 16 European countries at baseline, aged 15–60 years, who were examined for retinopathy by taking two-field 45° fundus photographs, which were centrally graded. Mortality and cardiovascular morbidity follow-up was assessed 6–8 years after baseline examination according to a standardized protocol.

RESULTS — After 7.9 years of follow-up, 64 patients had died and 128 patients had incident CVD. The age- and sex-adjusted hazard ratios (HRs) of all-cause mortality were 1.45 (95% CI 0.71–2.96) and 4.16 (1.96–8.84) in patients with nonproliferative and proliferative retinopathy at baseline, respectively. Adjustments for cardiovascular risk factors completely obliterated the association with nonproliferative retinopathy, whereas the association with proliferative retinopathy remained twofold increased, although nonsignificant. The age- and sex-adjusted HRs of incident CVD were 1.73 (1.15–2.60) and 2.05 (1.22–3.45) in patients with nonproliferative and proliferative retinopathy, respectively. After adjustments for cardiovascular risk factors, both associations were attenuated and lost statistical significance.

CONCLUSIONS — This study shows that type 1 diabetic patients with nonproliferative or proliferative retinopathy have an increased risk for all-cause mortality and incident CVD. The presence of cardiovascular risk factors explained the associations to a large extent, except for the associations with proliferative retinopathy, which suggests that other shared mechanisms may be involved.

Diabetes Care **28:1383–1389, 2005**

From the [1]Department of Ophthalmology, VU University Medical Center, Amsterdam, the Netherlands; the [2]Institute for Research in Extramural Medicine, VU University Medical Center, Amsterdam, the Netherlands; the [3]Department of Internal Medicine, Academic Hospital Maastricht, Maastricht, the Netherlands; the [4]Department of Epidemiology and Public Health, Royal Free and University College London Medical School, London, U.K.; the [5]Department of Ophthalmology, Odense University Hospital, Odense, Denmark; the [6]Diabetic Centre, Hippokration Hospital, Athens, Greece; the [7]Department of Endocrinology, University Hospital Gent, Gent, Belgium; the [8]Department of Internal Medicine, University of Turin, Turin, Italy; and the [9]International Centre for Circulatory Health & National Heart & Lung Institute, Imperial College London, London, U.K.

Address correspondence and reprint requests to Manon V. van Hecke, MD, Department of Ophthalmology, VU University Medical Center, P.O. Box 7057, 1007 MB Amsterdam, Netherlands. E-mail: m.vanhecke@vumc.nl.

Received for publication 3 December 2004 and accepted in revised form 14 March 2005.

Abbreviations: AER, albumin excretion rate; CVD, cardiovascular disease; ECG, electrocardiogram.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

© 2005 by the American Diabetes Association.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked "advertisement" in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

There is increasing evidence that micro- and macrovascular complications of diabetes share certain pathophysiological mechanisms. This may explain why microangiopathy has been associated with macroangiopathy and with mortality (1–10). For example, microalbuminuria has strongly and independently been associated with the development of cardiovascular disease (CVD) and mortality in type 2 diabetic patients (1–3,10). Further, retinopathy has also been associated with increased cardiovascular and all-cause mortality risk, particularly in type 2 diabetes (4–9). In type 1 diabetes, however, this association has been explored only in a limited fashion (4,11). Type 1 diabetes, though, offers a better opportunity to study the relationship between retinopathy and cardiovascular events than type 2 diabetes, because of a younger population with less confounding variables associated with the metabolic syndrome.

The pathophysiology underlying the association of retinopathy with CVD and mortality is not well understood. Cardiovascular risk factors, such as hypertension, dyslipidemia, and elevated HbA_{1c} level are also known as risk factors for the development of diabetic retinopathy (12,13), and thus, any association may simply reflect shared risk factors. Previous studies (4,7,14), however, reported that conventional cardiovascular risk factors can partly, but not entirely, account for the association between retinopathy and macrovascular disorders. Consequently, it can be hypothesized that, similar to the unknown mechanism by which microalbuminuria increases the risk of CVD (1), an unknown pathway may be involved in the relationship between retinopathy and macrovascular disorders. Importantly, if mechanistic pathways for any association for microalbuminuria and retinopathy are dissimilar, retinopathy could possibly reflect a new risk marker for CVD.

Downloaded from http://diabetesjournals.org/care/article-pdf/28/6/1383/659800/zdc00605001383.pdf by guest on 29 September 2022

Therefore, the aims of our study were to further explore the relationship of retinopathy with macrovascular disorders in type 1 diabetes and to investigate the role of cardiovascular risk factors in this association. Thus, we described the relationship of nonproliferative and proliferative retinopathy with all-cause mortality and CVD incidence (fatal and nonfatal together) during an 8-year follow-up of a large European sample of type 1 diabetic patients. In addition, we studied the role of known cardiovascular risk factors in these associations.

RESEARCH DESIGN AND METHODS

— The EURODIAB Prospective Complications Study is a follow-up of the EURODIAB IDDM Complications Study (15). Full details of the design, methods, and recruitment to the EURODIAB cohort have been published elsewhere (13,15,16). Baseline investigations were performed on 3,250 men and women with type 1 diabetes aged between 15 and 60 years and drawn from 31 centers in 16 European countries. The sampling frame contained all type 1 diabetic patients attending at least once in the last year for each center. Sample selection was stratified by age, sex, and duration of diabetes to ensure sufficient representation in all categories (15). Type 1 diabetes was defined as a diagnosis made before the age of 36 years, with a need for continuous insulin therapy within a year of diagnosis. Of those invited, 85% participated. Patients with a duration of diabetes <1 year and pregnant women were excluded. The local ethics committees approved this study at each center, and all persons provided written informed consent.

Ophthalmologic examination

Color retinal photographs were taken according to the EURODIAB protocol. This included a 45° macular and nasal field for each eye. Grading was performed by the retinopathy grading center at the Hammersmith Hospital of Imperial College (London) by observers masked to all information about the patient except an identification number (17). The grading system has been described in detail previously (17). In brief, retinal lesions were compared with standard photographs, and patients were assigned to one level out of a scale of six. High agreement was reached when compared against the standard seven-field stereo photograph protocol. The worst eye determined each patient's level of retinopathy. In this report, retinopathy is classified as nonproliferative or proliferative. Nonproliferative retinopathy was defined as the presence of one or more microaneurysms, hemorrhages, and/or hard exudates (17). Proliferative retinopathy was defined as any new vessels, fibrous proliferations, preretinal hemorrhage, vitreous hemorrhage, or photocoagulation scars (17). In addition, for the present study we also used a stricter classification of retinopathy to separately analyze the role of misclassification. In this stricter classification, nonproliferative retinopathy was defined as the presence of three or more microaneurysms, hemorrhages, and/or hard exudates.

Follow-up and outcomes

All patients were recalled for follow-up assessment 6–8 years later. At the time of the follow-up study, data on mortality and morbidity forms were collected from available hospital case notes or other sources of clinical data in every participating center, detailing cause of death or the presence or absence of severe complications at their most recent visit. When death certificates could not be obtained, information considering cause of death was reported by the physician or extracted from the hospital record. Cause of death could not be obtained for 23 of 64 deceased subjects because of legal restrictions.

Outcome variables were all-cause mortality and fatal and nonfatal CVD incidence. Causes of death were coded according to the ICD-9 classification and assigned to different categories, such as coronary heart disease, stroke, other CVD, non-CVD, and unknown. Two observers (N.C. and J.H.F.) separately allocated cause of death with 100% agreement. CVD was defined as a positive medical history of a cardiovascular event, including myocardial infarction, angina pectoris, coronary artery bypass graft and/or stroke, and/or ischemic changes on a conventional 12-lead electrocardiogram (ECG) (16) and was assessed at baseline and at follow-up examination. Two observers classified the ECG abnormalities according to the Minnesota Code. Any discrepancies between the two observers were adjudicated by a third. ECG abnormalities suggestive of probable ischemia consist of codes 1.1 and 1.2 (major Q/QS waves) and code 7.1 (complete left bundle branch block). Possible ischemia consists of code 1.3 for minor Q waves, codes 4.1, 4.2, and 4.3 for ST segment abnormalities, and codes 5.1, 5.2, and 5.3 for T wave abnormalities.

Additional measurements

Blood pressure was recorded in a sitting position with a random zero sphygmomanometer (Hawskley, Lancing, U.K.) as the mean of two measurements. Hypertension was defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg and/or the current use of blood pressure lowering–drugs (18). Baseline blood samples, from fasting patients where possible, had been sent to central laboratories for analysis. Measurements included triglycerides, total cholesterol, HDL cholesterol, and HbA_{1c}. Triglyceride (19) and cholesterol (20) concentration of plasma and the cholesterol concentration of HDL (21) were assayed by standard enzymatic methods (Boehringer Mannheim, East Sussex, U.K.) using a Cobas-Bio centrifugal analyzer (Roche, Welwyn Garden City, Herts, U.K.). HbA_{1c} was measured by an enzyme immunoassay (Dako, Ely, U.K.) using a monoclonal antibody raised against HbA_{1c} with a reference range of 2.9–4.8% (22). The intra-assay and interassay coefficients of variation were 2.3–2.4 and 2.6–5.0%, respectively. LDL cholesterol concentration was calculated from Friedewald's formula (23). Urinary albumin excretion was centrally determined with an immunoturbidimetric method, as previously described (24). Briefly, the albumin excretion rate (AER) was calculated from a timed 24-h urine collection, after excluding proteinuria due to urinary tract infection. The AER was defined as normal (<20 μg/min), microalbuminuria (≥20 μg/min and <200 μg/min), or macroalbuminuria (≥200 μg/min). Weight, height, and waist and hip circumferences were measured.

Statistical analysis

Baseline characteristics are presented as percentage, means ± SD, or median (interquartile range) in the case of a skewed distribution by nonproliferative and proliferative retinopathy status. Overall group differences in continuous variables were tested with ANOVA. Pearson's χ^2 test was used for differences in categorical measures. *P* values <0.05 were considered statistically significant. The fol-

Downloaded from http://diabetesjournals.org/care/article-pdf/28/6/1383/659800/zdc00605001383.pdf by guest on 29 September 2022

Table 1—*Baseline characteristics, 8-year mortality, and CVD incidence according to retinopathy status in patients with type 1 diabetes*

	No retinopathy	Nonproliferative retinopathy	Proliferative retinopathy	*P* value
n	1,210	795	232	
Baseline				
Age (years)	29 ± 9	35 ± 10	39 ± 10	<0.001
Sex (% male)	49	55	48	0.02
Duration diabetes (years)*	8.4 (5.1–13.2)	17.0 (12.8–22.6)	24.0 (19.2–28.4)	<0.001
HbA_{1c} (%)	6.5 ± 2.0	6.8 ± 1.7	6.8 ± 1.9	0.001
Hypertension (%)	5	16	38	<0.001
Systolic blood pressure (mmHg)	116 ± 14	123 ± 19	131 ± 21	<0.001
Diastolic blood pressure (mmHg)	74 ± 11	76 ± 11	79 ± 11	<0.001
BMI (kg/m^2)	23.1 ± 2.8	24.0 ± 2.8	23.9 ± 2.7	<0.001
Waist-to-hip ratio	0.85 ± 0.13	0.86 ± 0.11	0.86 ± 0.12	0.091
Waist circumference (cm)	78.2 ± 9.7	81.8 ± 9.6	80.7 ± 10.4	<0.001
Cholesterol (mmol/l)	5.1 ± 1.0	5.4 ± 1.1	5.7 ± 1.3	<0.001
Triglycerides (mmol/l)*	0.9 (0.7–1.2)	1.0 (0.7–1.4)	1.1 (0.8–1.6)	<0.001
LDL cholesterol (mmol/l)	3.2 ± 0.9	3.4 ± 1.0	3.6 ± 1.1	<0.001
HDL cholesterol (mmol/l)	1.5 ± 0.4	1.5 ± 0.4	1.4 ± 0.4	0.066
AER (μg/min)*	0.9 (0.6–1.7)	1.2 (0.7–3.0)	6.0 (1.2–37.4)	<0.001
Microalbuminuria (%)	18	25	30	<0.001
Macroalbuminuria (%)	2	9	33	<0.001
Height (cm)	169.5 ± 9.7	169.2 ± 9.6	166.3 ± 8.7	<0.001
Prior CVD (%)	6	9	18	<0.001
Follow-up				
All-cause mortality	18 (1.5)	24 (3.0)	22 (9.5)	<0.001
Nonfatal CVD incidence†	43 (4.1)	58 (8.6)	21 (11.7)	<0.001
Fatal and nonfatal CVD incidence†	43 (4.1)	60 (8.9)	25 (13.6)	<0.001

Data are means ± SD, *n* (%), or median (interquartile range) in case of skewed distribution, unless otherwise indicated. *Log transformed because of skewed distribution. †For these analyses, we used 1,914 subjects without prevalent CVD and with available information on morbidity follow-up status. *P* value: test for trend (ANOVA) for continuous variables or Pearson's χ^2 test for categorical measures.

low-up duration for mortality was calculated as the time between the baseline examination and date of death, date of loss to follow-up, or date of the follow-up examination. Follow-up duration for fatal and nonfatal CVD incidence was calculated as the time between the baseline examination and date of first event (myocardial infarction, angina pectoris, coronary artery bypass graft, or stroke), date of abnormal ECG finding suggestive of ischemia, date of loss to follow-up, or date of follow-up examination. Kaplan-Meier survival curves for subjects without retinopathy or with nonproliferative or proliferative retinopathy were plotted for all-cause mortality. Differences between the curves were tested by the log rank test. Cox's proportional hazard analyses were used to analyze the association of nonproliferative and proliferative retinopathy at baseline with all-cause mortality and incidence of fatal and nonfatal CVD. We first adjusted for age and sex only. Then, associations were adjusted one by one for possible contributing covariates to demonstrate their individual role in accounting for any elevated risk. Finally, a multivariate model was created in order to study the independent predictive power of nonproliferative and proliferative retinopathy for all-cause mortality and fatal and nonfatal CVD incidence. Data are presented as hazard ratios (HRs) (which can be interpreted as relative risks) with a 95% CI. All analyses were performed in SPSS 10.1 for Windows 98.

RESULTS — Of the 3,250 patients recruited at baseline, 2,237 had usable photographs and information on vital status and were included in the present study. We excluded 771 subjects with missing fundus photographs and 463 subjects with missing vital status at follow-up. Vital status was not obtained for 463 persons because of the following reasons: 4 local centers did not participate in the prospective study ($n = 437$), 8 patients did not fulfill the inclusion criteria, and 18 had an unknown vital status. Subjects with missing fundus photographs and/or missing vital status at follow-up had significantly higher HbA_{1c} levels, larger waist circumferences, higher diastolic blood pressure levels, a higher prevalence of prior CVD, and a less favorable lipid profile.

For the analyses with incident CVD as outcome variable, we excluded subjects with missing follow-up morbidity data ($n = 134$) and/or prevalent CVD ($n = 174$) and/or unknown cause of death ($n = 23$), resulting in 1,914 individuals with complete data. Baseline distribution of risk factors did not differ between patients with known and missing causes of death, but the group with missing morbidity data at follow-up had higher systolic blood pressure levels, larger waist circumferences, and higher triglyceride levels. Table 1 shows the baseline characteristics, 8-year mortality, and fatal and nonfatal CVD incidence according to baseline retinopathy status.

Retinopathy and all-cause mortality

After a median follow-up of 7.5 years (range 7.0–7.9), 64 patients died. Among

Downloaded from http://diabetesjournals.org/care/article-pdf/28/6/1383/659800/zdc00605001383.pdf by guest on 29 September 2022

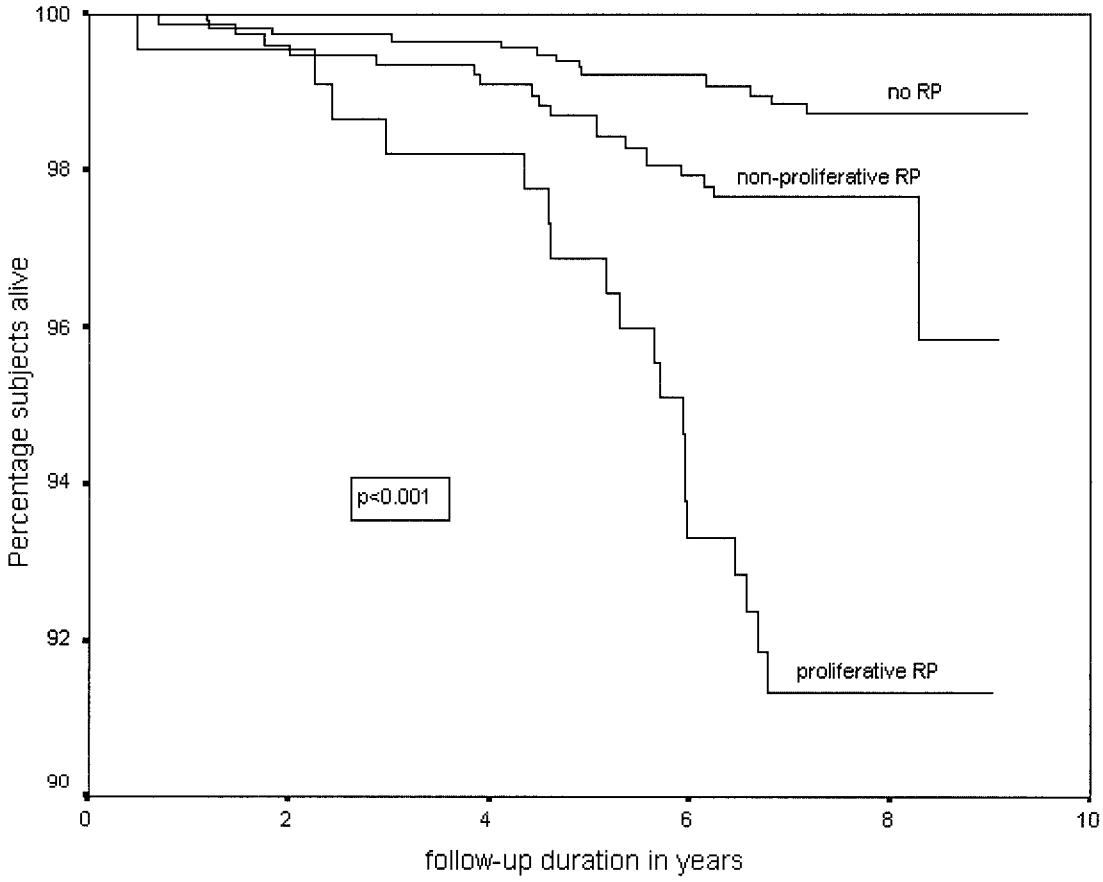

Figure 1—*All-cause mortality according to baseline retinopathy (RP) status in type 1 diabetes.*

patients with no, nonproliferative, and proliferative retinopathy, the percentages of deaths were 1.5% ($n = 18$; two cardiovascular, nine noncardiovascular, seven unknown), 3.0% ($n = 24$; 6, 9, 9, respectively), and 9.5% ($n = 22$; 8, 7, 7, respectively) (Table 1).

The Kaplan-Meier curves in Fig. 1 show that all-cause mortality was significantly higher in patients with proliferative retinopathy than in patients with nonproliferative retinopathy and subjects without retinopathy ($P < 0.001$). All-cause mortality in patients with nonproliferative retinopathy was also significantly elevated compared with patients without retinopathy ($P = 0.034$). The age- and sex-adjusted HRs of all-cause mortality were 1.45 (95% CI 0.71–2.96) and 4.16 (1.96–8.84) in patients with nonproliferative and proliferative retinopathy, respectively, compared with patients without retinopathy (Table 2). The increased mortality risks associated with nonproliferative and proliferative retinopathy were considerably attenuated by adjustment for lipids and AER and, for nonproliferative retinopathy, was completely obliterated in the multivariate model, while remaining large (2.06), but statistically nonsignificant, in proliferative retinopathy (Table 2).

Retinopathy and incident CVD

After a median follow-up of 7.4 years (range 6.9–7.9), 128 patients had incident CVD (either fatal or nonfatal). Among patients with no, nonproliferative, and proliferative retinopathy, the percentages of cases were 4.1% ($n = 43$; 2 fatal, 43 nonfatal), 8.9% ($n = 60$; 6 fatal, 58 nonfatal), and 13.6% ($n = 25$; 8 fatal, 21 nonfatal).

The age- and sex-adjusted HRs of incident CVD were 1.73 (95% CI 1.15–2.60) and 2.05 (1.22–3.45) in patients with nonproliferative and proliferative retinopathy compared with patients without retinopathy, respectively (Table 2). The increased CVD risks associated with nonproliferative and proliferative retinopathy were explained to some extent, but not entirely, by other risk factors, notably HbA_{1c}, hypertension, and albumin excretion (Table 2).

Additional analyses

To evaluate possible misclassification, we repeated the analyses with a more strict classification of retinopathy of three or more abnormalities. This did not materially change the results (data not shown), indicating misclassification was limited. The analyses for all-cause mortality were repeated after exclusion of patients with prior CVD at baseline. This again did not materially change the results (data not shown).

CONCLUSIONS — The present study shows that both nonproliferative and proliferative retinopathy were predictive of subsequent all-cause mortality and cardiovascular events in type 1 diabetic patients. After adjustment for cardiovascular risk factors, the increased risk for all-cause mortality disappeared in subjects with nonproliferative retinopathy but remained twofold greater in those with proliferative retinopathy. Lipid lev-

Downloaded from http://diabetesjournals.org/care/article-pdf/28/6/1383/659800/zdc00605001383.pdf by guest on 29 September 2022

Table 2—*Age- and sex-adjusted hazard ratios for all-cause mortality and fatal and nonfatal CVD associated with nonproliferative and proliferative retinopathy in type 1 diabetes*

	All-cause mortality		Fatal and nonfatal CVD	
	Nonproliferative retinopathy	Proliferative retinopathy	Nonproliferative retinopathy	Proliferative retinopathy
Model 1 and added variables	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Model 1: retinopathy, age, and sex	1.45 (0.71–2.96)	4.16 (1.96–8.84)	1.73 (1.15–2.60)	2.05 (1.22–3.45)
One-by-one adjustment				
Model 1 and diabetes duration	1.74 (0.83–3.68)	5.90 (2.46–14.14)	1.75 (1.13–2.69)	2.10 (1.17–3.77)
Model 1 and HbA_{1c}	1.38 (0.68–2.83)	3.99 (1.87–8.51)	1.65 (1.09–2.49)	1.98 (1.18–3.34)
Model 1 and hypertension	1.33 (0.65–2.74)	3.32 (1.52–7.26)	1.60 (1.06–2.42)	1.79 (1.05–3.06)
Model 1 and BMI	1.51 (0.74–3.08)	4.28 (2.02–9.10)	1.74 (1.15–2.62)	2.05 (1.22–3.46)
Model 1 and waist-to-hip ratio	1.45 (0.71–2.96)	4.12 (1.94–8.76)	1.72 (1.15–2.60)	2.10 (1.25–3.52)
Model 1 and triglycerides	1.24 (0.60–2.55)	3.73 (1.77–7.87)	1.69 (1.12–2.55)	2.00 (1.19–3.38)
Model 1 and LDL cholesterol	0.79 (0.33–1.88)	2.78 (1.18–6.56)	1.91 (1.18–3.10)	2.57 (1.41–4.67)
Model 1 and non-HDL cholesterol	1.19 (0.52–2.71)	3.65 (1.55–8.57)	1.73 (1.15–2.61)	2.03 (1.20–3.44)
Model 1 and AER	1.10 (0.52–2.32)	3.09 (1.40–6.82)	1.60 (1.05–2.44)	1.79 (1.03–3.09)
Model 1 and smoking status	1.42 (0.70–2.90)	4.35 (2.05–9.25)	1.72 (1.14–2.58)	2.10 (1.24–3.54)
Model 1 and prior CVD	1.43 (0.70–2.93)	3.89 (1.81–8.36)	1.66 (1.10–2.51)	2.14 (1.27–3.60)
Multivariate model				
Model 1 and diabetes duration, HbA_{1c}, hypertension, BMI, LDL cholesterol, AER, and prior CVD	0.54 (0.19–1.53)	2.06 (0.63–6.73)	1.30 (0.74–2.29)	1.63 (0.80–3.33)

HR (95% CI) for all-cause mortality and fatal and nonfatal CVD analyzed by Cox's proportional hazards analyses.

els and AER explained a considerate part of the association between retinopathy and mortality. Surprisingly, HbA_{1c} and diabetes duration, both important risk factors for retinopathy as well as mortality in the EURODIAB study (10,13), did not contribute to the relation of retinopathy and mortality. The increased risk for CVD in people with nonproliferative or proliferative retinopathy was attenuated but not completely explained by adjustment for cardiovascular risk factors, in particular HbA_{1c}, hypertension, and AER.

The present findings support results from previous studies (4,6–9,11,25) in type 1 and type 2 diabetes that demonstrated that retinopathy is positively associated with mortality and cardiovascular events and that these associations can be explained to an important extent, but not entirely, by other cardiovascular risk factors (4,8). The Wisconsin Epidemiologic Study of Diabetic Retinopathy, the only prospective study of retinopathy and mortality in a type 1 diabetic population, showed after 16 and 20 years follow-up a slightly increased risk for CVD and mortality associated with retinopathy (4,11), which is consistent with our results. In the present European study, the association with all-cause mortality was relatively stronger but lost statistical significance in the multivariate model due to small sample sizes. Moreover, the number of fatal CVD cases was too small for separate analyses. In the Atherosclerosis Risk in Communities study (26), diabetic retinopathy was not associated with any clinical manifestation of atherosclerosis, such as stroke, coronary heart disease, and peripheral artery disease. However, these were cross-sectional results, and only one fundus photograph was taken of each participant, which may have influenced the associations.

Our finding that proliferative retinopathy was more strongly associated with all-cause mortality than nonproliferative retinopathy is consistent with other studies (4,6,8) in type 2 diabetic patients and suggests that proliferative retinopathy is a stronger risk marker than nonproliferative retinopathy. Risk of fatal and nonfatal CVD, however, was almost similar in both nonproliferative and proliferative retinopathy. The stronger association of proliferative retinopathy with all-cause mortality (fourfold) than with combined fatal and nonfatal cardiovascular events (twofold) is striking, given that we hypothesized that any association should be related to vascular disorders. This discrepancy may be partly due to, first, the considerable proportion of deaths with unknown causes, which are likely to be cardiovascular in origin. Second, the majority of cardiovascular events were nonfatal and based on criteria such as ECG abnormalities, which may result in a degree of misclassification. Life and death status is clearly easier to classify correctly.

In contrast to previous reports (4,7,8) in type 2 diabetic patients, the increased risk of all-cause mortality and incident CVD associated with nonproliferative retinopathy was completely obliterated after adjustment for known cardiovascular risk factors. However, proliferative retinopathy was associated with a twofold increased risk for all-cause mortality and CVD, although nonsignificant. Thus, proliferative retinopathy may reflect other pathways than the conventional cardiovascular risk factors leading to an increased risk of mortality or CVD. Advanced glycated end products could play an important role in the relationship between retinopathy and cardiovascular outcomes, as advanced glycated end products are reported to be involved in the pathogenesis of retinopathy and atherosclerosis (27,28). Other unidentified mechanisms could include endothelial

Downloaded from http://diabetesjournals.org/care/article-pdf/28/6/1383/659800/zdc00605001383.pdf by guest on 29 September 2022

dysfunction and inflammatory activity, both reported to be associated with microvascular and macrovascular disorders (29–33). These possibilities require further study.

The EURODIAB Prospective Complications Study offers a unique possibility to study complications of type 1 diabetes, as it provides a large, multicenter, European cohort of type 1 diabetic patients attending a clinic minimally once a year and where the same standardized methods were used in each center. Furthermore, type 2 diabetes is often associated with numerous other risk factors for CVD in the, often elderly, patients affected, so that disentangling analysis may remain open to imprecision. Type 1 diabetes may offer a "cleaner" model to study such relationships. However, since cardiovascular events are relatively rare among these younger patients, a similar study could be carried out only in such large population as the one studied prospectively by the EURODIAB Prospective Complications Study.

Limitations were also present in this study. First, of the baseline population, 31% had missing fundus photographs and/or were lost to follow-up, and 14% had missing morbidity data. These individuals with missing data of mortality and morbidity follow-up and/or fundus photographs at baseline had a more atherogenic profile. This may have lead to an underestimation of the true association of retinopathy with mortality and CVD incidence. Second, the release of confidential cause of death data was difficult due to legal restrictions in a number of countries, which led to a relatively large number of unknown causes of death. Finally, the measurement at baseline of all covariates used in this study was done only once. Therefore, the role of residual confounding related to imprecision of measurements of covariates due to this single measurement, leading to an underestimation of the confounding role of a covariate, cannot be discounted. Nevertheless, the twofold increased risk of total mortality associated with proliferative retinopathy despite multivariate adjustments suggests that residual confounding cannot wholly account for our findings.

In conclusion, we have shown that nonproliferative and proliferative retinopathy in type 1 diabetes are associated with an increased risk of all-cause mortality and incident CVD. Adjustments for cardiovascular risk factors completely obliterated the association with nonproliferative retinopathy, whereas the association with proliferative retinopathy remained increased, although nonsignificant. These data suggest that mechanisms other than shared cardiovascular risk factors may be involved in the relationship between retinopathy and CVD and mortality.

Acknowledgments— This work was generously supported by grants from the Wellcome Trust, European Community, and Diabetes U.K. We thank all the investigators and all the patients who took part.

The EURODIAB Prospective Complications Study Group: B. Karamanos, A. Kofinis, K. Petrou, Hippokration Hospital, Athens, Greece. F. Giorgino, G. Picca, A. Angarano, G. De Pergola, L. Laviola, R. Giorgino, Department of Emergency and Organ Transplantation, Internal Medicine, Endocrinology and Metabolic Diseases, University of Bari, Bari, Italy. C. Ionescu-Tirgoviste, A. Coszma, C. Guja, Clinic of Diabetes, Nutrition & Metabolic Diseases, Bucharest, Romania. M. Songini, A. Casu, M. Pedron, S. Pintus, M. Fossarello, Diabetes Unit Ospedale San Michele, Cagliari, Italy. J.B. Ferriss, G. Grealy, D.O. Keefe, Cork University Hospital, Cork, Ireland. M. Toeller, C. Arden, Diabetes Research Institute, Heinrich-Heine University, Dusseldorf, Germany. R. Rottiers, C. Tuyttens, H. Priem, University Hospital of Gent, Gent, Belgium. P. Ebeling, M. Kylliäinen, V.A. Koivisto, University Hospital of Helsinki, Helsinki, Finland. B. Idzior-Walus, J. Sieradzki, K. Cyganek, B. Solnica, Department of Metabolic Diseases, Jagiellonian University, Krakow, Poland. H.H.P.J. Lemkes, J.C. Lemkes-Stuffken, Leiden University Medical Centre, Leiden, The Netherlands. J. Nunes-Correa, M.C. Rogado, L. Gardete-Correia, M.C. Cardoso, A. Silva, J. Boavida, M. Machado Sa Marques, Portuguese Diabetic Association, Lisbon, Portugal. G. Michel, R. Wirion, S. Cardillo, Centre Hospitalier, Luxembourg. G. Pozza, R. Mangili, V. Asnaghi, Ospedale San Raffaele, Milan, Italy. E. Standl, B. Schaffler, H. Brand, A. Harms, City Hospital Schwabing, Munich, Germany. D. Ben Soussan, O. Verier-Mine, P. Fallas, M.C. Fallas, Centre Hospitalier de Valenciennes, Valenciennes, France. J.H. Fuller, J. Holloway, L. Asbury, D.J. Betteridge, University College London, London, U.K. G. Cathelineau, A. Bouallouche, B. Villatte Cathelineau, Hospital Saint-Louis, Paris, France. F. Santeusanio, G. Rosi, V. D'Alessandro, C. Cagini, P. Bottini, G.P. Reboldi, Diaprtimento di Medicina Interna, Perugia, Italy R. Navalesi, G. Penno, S. Bandinelli, R. Miccoli, M. Nannipieri, Dipartimento di Endocrinologia e Metabolismo, Pisa, Italy. G. Ghirlanda, C. Saponara, P. Cotroneo, A. Manto, A. Minnella, Universita Cattolica del Sacro Cuore, Rome, Italy. J.D. Ward, S. Tesfaye, S. Eaton, C. Mody, Royal Hallamshire Hospital, Sheffield, U.K. M. Borra, P. Cavallo Perin, S. Giunti, G. Grassi, G.F. Pagano, M. Porta, R. Sivieri, F. Vitelli, M. Veglio Dipartimento di Medicina Interna, Università di Torino and ASO CTO/CRF/Maria Adelaide, Turin, Italy. N. Papazoglou, G. Manes, General Hospital Papageorgiou of Thessaloniki, Thessaloniki, Greece. M. Muggeo, M. Iagulli, V. Cacciatori, V Cattedra di Malattie del Metabolismo, Verona, Italy. K. Irsigler, H. Abrahamian, Hospital Vienna Lainz, Vienna, Austria. S. Walford, J. Sinclair, S. Hughes, V. McLelland, J. Ward, New Cross Hospital, Wolverhampton, U.K. G. Roglic, Z. Metelko, Z.R. Pepeonik, Vuk Vrhovac Institute for Diabetes, Zagreb, Croatia.

Steering committee members: J.H. Fuller (London), B. Karamanos, Chairman (Athens), A.-K. Sjolie (Aarhus), N. Chaturvedi (London), M. Toeller (Dusseldorf), G. Pozza, co-chairman (Milan), B. Ferriss (Cork), M. Porta (Turin), R. Rottiers (Gent), G Michel (Luxembourg). Coordinating center: J.H. Fuller, N. Chaturvedi, J. Holloway, D. Webb, L. Asbury, University College London, London, U.K.

Central laboratories: G.-C. Viberti, R. Swaminathan, P. Lumb, A. Collins, S. Sankaralingham, Guy's and St. Thomas Hospital, London, U.K.

Retinopathy grading center: S. Aldington, T. Mortemore, H. Lipinski, Royal Postgraduate Medical School of Imperial College London, London, U.K.

References

1. Jager A, Kostense PJ, Ruhe HG, Heine RJ, Nijpels G, Dekker JM, Bouter LM, Stehouwer CD: Microalbuminuria and peripheral arterial disease are independent predictors of cardiovascular and all-cause mortality, especially among hypertensive subjects: five-year follow-up of the Hoorn Study. *Arterioscler Thromb Vasc Biol* 19: 617–624, 1999
2. Dinneen SF, Gerstein HC: The association of microalbuminuria and mortality in non-insulin-dependent diabetes mellitus: a systematic overview of the literature. *Arch Intern Med* 157:1413–1418, 1997
3. Neil A, Hawkins M, Potok M, Thorogood M, Cohen D, Mann J: A Prospective population-based study of microalbuminuria as a predictor of mortality in NIDDM. *Diabetes Care* 16:996–1003, 1993
4. Klein R, Klein BEK, Moss SE, Cruickshanks KJ: Association of ocular disease and mortality in a diabetic population. *Arch Ophthalmol* 117:1487–1495, 1999
5. Rajala U, Pajunpaa H, Koskela P, Keinanen-Kiukaanniemi S: High cardiovascular disease mortality in subjects with visual impairment caused by diabetic

Downloaded from http://diabetesjournals.org/care/article-pdf/28/6/1383/659800/zdc00605001383.pdf by guest on 29 September 2022

retinopathy. *Diabetes Care* 23:957–961, 2000
6. Hanis CL, Chu HH, Lawson K, Hewett-temmett D, Barton SA, Schull WJ, Garcia CA: Mortality of Mexican Americans with NIDDM: retinopathy and other predictors in Starr County, Texas. *Diabetes Care* 16: 82–89, 1993
7. van Hecke MV, Dekker JM, Nijpels G, Moll AC, van Leiden HA, Heine RJ, Bouter LM, Stehouwer CDA, Polak BCP: Retinopathy is associated with cardiovascular and all-cause mortality in both diabetic and nondiabetic subjects: the Hoorn Study (Letter). *Diabetes Care* 26:2958, 2003
8. Miettinen H, Haffner SM, Lehto S, Ronnemaa T, Pyorala K, Laakso M: Retinopathy predicts coronary heart disease events in NIDDM patients. *Diabetes Care* 19:1445–1448, 1996
9. Klein R, Moss SE, Klein BEK, Demets DL: Relation of ocular and systemic factors to survival in diabetes. *Arch Intern Med* 149: 266–272, 1989
10. Soedamah-Muthu SS, Chaturvedi N, Toeller M, Ferriss B, Reboldi P, Michel G, Manes C, Fuller JH: Risk factors for coronary heart disease in type 1 diabetic patients in Europe: the EURODIAB Prospective Complications Study. *Diabetes Care* 27:530–537, 2004
11. Klein BE, Klein R, McBride PE, Cruickshanks KJ, Palta M, Knudtson MD, Moss SE, Reinke JO: Cardiovascular disease, mortality, and retinal microvascular characteristics in type 1 diabetes: Wisconsin epidemiologic study of diabetic retinopathy. *Arch Intern Med* 164:1917–1924, 2004
12. van Leiden HA, Dekker JM, Moll AC, Nijpels G, Heine RJ, Bouter LM, Stehouwer CDA, Polak BCP: Risk factors for incident retinopathy in a diabetic and nondiabetic population: the Hoorn study. *Arch Ophthalmol* 121:245–251, 2003
13. Chaturvedi N, Sjoelie AK, Porta M, Aldington SJ, Fuller JH, Songini M, Kohner EM: Markers of insulin resistance are strong risk factors for retinopathy incidence in type 1 diabetes. *Diabetes Care* 24:284–289, 2001
14. Fuller JH, Stevens LK, Wang SL: Risk factors for cardiovascular mortality and morbidity: the WHO Mutinational Study of Vascular Disease in Diabetes. *Diabetologia* 44 (Suppl. 2):S54–S64, 2001
15. Stephenson J, Fuller JH: Microvascular and acute complications in IDDM patients: the EURODIAB IDDM Complications Study. *Diabetologia* 37:278–285, 1994
16. Koivisto VA, Stevens LK, Mattock M, Ebeling P, Muggeo M, Stephenson J, Idzior-Walus B: Cardiovascular disease and its risk factors in IDDM in Europe: EURODIAB IDDM Complications Study Group. *Diabetes Care* 19:689–697, 1996
17. Aldington SJ, Kohner EM, Meuer S, Klein R, Sjolie AK: Methodology for retinal photography and assessment of diabetic retinopathy: the EURODIAB IDDM Complications Study. *Diabetologia* 38:437–444, 1995
18. Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: The sixth report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure. *Arch Intern Med* 157:2413–2446, 1997
19. Bucolo G, David H: Quantitative determination of serum triglycerides by use of enzymes. *Clin Chem* 19:476–482, 1973
20. Siedel J, Hagele EO, Ziegenhorn J, Wahlefeld AW: Reagent for the enzymatic determination of serum total cholesterol with improved lipolytic efficiency. *Clin Chem* 29:1075–1080, 1983
21. Warnick GR, Albers JJ: Comprehensive evaluation of heparin manganese precipitation procedure for estimating high-density lipoprotein cholesterol. *J Lipid Res* 19:65–76, 1978
22. John WG, Gray MR, Bates DL, Beacham JL: Enzyme immunoassay: a new technique for estimating hemoglobin A1C. *Clin Chem* 39:663–666, 1993
23. Friedewald WT, Levy RI, Fredrickson DS: Estimation of concentration of low-density lipoprotein cholesterol in plasma, without use of preparative ultracentrifuge. *Clin Chem* 18:499–502, 1972
24. Kearney EM, Mount JN, Watts GF, Slavin BM, Kind PRN: Simple immunoturbidimetric method for determining urinary albumin at low concentrations using Cobas-Bio centrifugal analyzer. *J Clin Pathol* 40:465–468, 1987
25. Klein R, Marino EK, Kuller LH, Polak JF, Tracy RP, Gottdiener JS, Burke GL, Hubbard LD, Boineau R: The relation of atherosclerotic cardiovascular disease to retinopathy in people with diabetes in the Cardiovascular Health Study. *Br J Ophthalmol* 86:84–90, 2002
26. Klein R, Sharrett AR, Klein BEK, Moss SE, Folsom AR, Wong TY, Brancati FL, Hubbard LD, Couper D: The association of atherosclerosis, vascular risk factors, and retinopathy in adult's with diabetes: the Atherosclerosis Risk in Communities Study. *Ophthalmology* 109:1225–1234, 2002
27. Chakrabarti S, Cukiernik M, Hileeto D, Evans T, Chen S: Role of vasoactive factors in the pathogenesis of early changes in diabetic retinopathy. *Diabetes Metab Res Rev* 16:393–407, 2000
28. Singh R, Barden A, Mori T, Beilin L: Advanced glycation end-products: a review. *Diabetologia* 44:129–146, 2001
29. Ross R: Atherosclerosis: an inflammatory disease. *N Engl J Med* 340:115–126, 1999
30. Jager A, van Hinsbergh VWM, Kostense PJ, Emeis JJ, Yudkin JS, Nijpels G, Dekker JM, Heine RJ, Bouter LM, Stehouwer CDA: von Willebrand factor, C-reactive protein, and 5-year mortality in diabetic and nondiabetic subjects: the Hoorn study. *Arterioscler Throm Vasc Biol* 19: 3071–3078, 1999
31. Stehouwer CDA, Gall MA, Twisk JWR, Knudsen E, Emeis JJ, Parving HH: Increased urinary albumin excretion, endothelial dysfunction, and chronic low-grade inflammation in type 2 diabetes: progressive, interrelated, and independently associated with risk of death. *Diabetes* 51:1157–1165, 2002
32. Matsumoto K, Sera Y, Ueki Y, Inukai G, Niiro E, Miyake S: Comparison of serum concentrations of soluble adhesion molecules in diabetic microangiopathy and macroangiopathy. *Diabet Med* 19:822–826, 2002
33. Schram MT, Chaturvedi N, Schalkwijk C, Giorgino F, Ebeling P, Fuller JH, Stehouwer CD: Vascular risk factors and markers of endothelial function as determinants of inflammatory markers in type 1 diabetes: the EURODIAB Prospective Complications Study. *Diabetes Care* 26:2165–2173, 2003

Downloaded from http://diabetesjournals.org/care/article-pdf/28/6/1383/659800/zdc00605001383.pdf by guest on 29 September 2022