ORIGINAL INVESTIGATION

Cardiovascular Disease, Mortality, and Retinal Microvascular Characteristics in Type 1 Diabetes

Wisconsin Epidemiologic Study of Diabetic Retinopathy

Barbara E. K. Klein, MD; Ronald Klein, MD; Patrick E. McBride, MD; Karen J. Cruickshanks, PhD; Mari Palta, PhD; Michael D. Knudtson, MS; Scot E. Moss, MA; Jennifer O. Reinke, BA

Background: Diabetic retinopathy and proteinuria, manifestations of microvascular abnormalities, occur early in the course of diabetes mellitus; in contrast, macrovascular cardiovascular complications usually occur later. Retinal vessel characteristics may be informative about risk of cardiovascular disease in persons with diabetes. We evaluated this in a longitudinal cohort study of persons with type 1 diabetes.

Methods: The population consisted of persons with type 1 diabetes who were receiving care in 11 counties in Wisconsin. Subjects (n=996) were examined at baseline (1980-1982), and 4, 10, 14, and 20 years later. Evaluations included medical history and measurements of height, weight, blood pressure, and glycosylated hemoglobin. Fundus photographs were graded for diabetic retinopathy at baseline, and the same photographs were graded later for the diameters of retinal blood vessels. At each examination, a history of cardiovascular disease events since the last examination (and prior to baseline) was obtained. Mortality was monitored yearly.

Results: The 20-year age-adjusted cumulative incidences were 18.1% for angina, 14.8% for myocardial infarction, and 5.9% for stroke. Severity of diabetic retinopathy was associated with angina and stroke. Arteriovenous ratio was associated with myocardial infarction. Of 273 deaths, 176 involved heart disease. The severity of retinopathy and arteriovenous ratio was associated with heart disease mortality. Nephropathy was more informative about the cardiovascular end points than were the blood vessel characteristics.

Conclusions: Incidences of cardiovascular disease, including mortality, were common in people with type 1 diabetes during a 20-year interval. Retinal vascular characteristics were associated with these end points, but this association was confounded by nephropathy.

Arch Intern Med. 2004;164:1917-1924

From the Departments of Ophthalmology and Visual Sciences (Drs B. E. K. Klein, R. Klein, and Cruickshanks, Messrs Knudtson and Moss, and Ms Reinke), Medicine (Dr McBride), and Population Health Sciences (Drs Cruickshanks and Palta), University of Wisconsin Medical School, Madison.
Dr McBride has received honoraria from GlaxoSmithKline, Bristol-Myers Squibb Co, Kos Pharmaceuticals Inc, Merck & Co Inc, and Pfizer Inc.

CARDIOVASCULAR DISEASE IS a well-known complication of diabetes,[1-5] and microvascular characteristics have been hypothesized to contribute to it.[6] Some studies have shown that generalized and focal narrowing of retinal arterioles and arteriovenous crossing changes were associated with increased cardiovascular disease in persons with hypertension.[7-9] The odds of having a cerebral infarction was 2.3 (95% confidence interval, 1.2-4.4) for low arteriovenous ratio (AVR).[10] The purpose of the current study is to describe the incidence of cardiovascular outcomes and of heart disease mortality as related to diabetic retinopathy and ratio of arteriole to venule diameters as graded from images taken in 1980 to 1982 in persons with type 1 diabetes mellitus.

METHODS

POPULATION

Of 1210 persons receiving care for type 1 diabetes in a defined area of Wisconsin in 1979 to 1980, 996 participated in a study of diabetic retinopathy.[11] The institutional human subjects committee approved the study, and informed consent was obtained from each participant at each study visit. The participants had C-peptide levels less than 0.9 ng/mL (0.3 nmol/L).[12] The baseline evaluation included a medical history; measurements of blood pressure, glycosylated hemoglobin,[13] height, and weight; dilation of the pupil; and photography of the ocular fundus of each eye. Because we were interested in associations of observations taken at one time to subsequent end points, we used only baseline measures of risk variables.

Fundus photographs were graded for lesions of diabetic retinopathy by means of a modification of the Early Treatment Diabetic

©2004 American Medical Association. All rights reserved.

Downloaded From: http://archinte.jamanetwork.com/ on 07/21/2017

Table 1. Baseline Risk Factors Considered in Multivariable Models of Cardiovascular Disease

Risk Factor	Angina			Myocardial Infarction			Stroke		
	No. of Persons	20-y Incidence, %	*P* Value*	No. of Persons	20-y Incidence, %	*P* Value*	No. of Persons	20-y Incidence, %	*P* Value*
Age, y									
0-9.9	27	0.0	<.001	27	0.0	<.001	27	0.0	<.001
10.0-14.9	85	4.0		85	4.0		85	1.3	
15.0-19.9	152	7.9		152	5.9		151	0.0	
20.0-29.9	294	11.7		293	10.6		292	3.3	
30.0-44.9	254	24.3		255	18.4		260	8.1	
≥45.0	94	50.1		95	42.0		103	20.0	
Sex									
Female	443	19.1	.06	447	13.0	.72	452	4.0	.17
Male	463	13.5		460	13.7		466	6.5	
Duration of diabetes, y									
0-4.9	169	7.1	<.001	169	2.6	<.001	168	0.0	<.001
5.0-9.9	242	6.8		242	6.9		241	2.8	
10.0-14.9	168	18.0		167	12.4		169	1.9	
15.0-19.9	121	21.5		120	20.2		122	5.3	
20.0-29.9	142	29.2		145	28.4		148	17.8	
≥30.0	64	53.1		64	34.2		70	14.3	
GHb, %									
5.6-9.4	225	13.4	.87	226	9.5	.08	228	2.9	.02
9.5-10.5	210	19.2		208	15.2		212	3.5	
10.6-12.0	215	20.5		215	15.0		221	8.2	
12.1-19.5	215	13.3		217	15.9		217	7.1	
SBP, mm Hg									
78-110	224	9.9	<.001	224	8.3	<.001	226	3.5	.01
111-120	249	11.3		247	6.9		252	3.9	
121-134	234	16.8		235	13.0		236	4.8	
135-221	192	32.0		194	31.6		197	10.9	
DBP, mm Hg									
42-71	236	11.7	.02	236	8.3	.03	240	4.5	.67
72-78	228	18.3		231	15.5		232	5.4	
79-85	211	14.6		210	13.4		213	5.6	
86-117	222	20.8		221	17.0		224	5.5	
Hypertension									
Absent	730	14.0	<.001	732	10.7	<.001	740	4.3	.01
Present	170	28.0		169	28.2		172	10.1	
Pulse pressure, mm Hg									
<34	218	10.0	<.001	218	8.0	<.001	221	3.0	.003
34-42	255	15.8		254	11.1		255	3.8	
43-55	243	12.6		244	9.6		247	5.6	
>55	181	30.8		182	29.7		186	10.1	

(continued)

Retinopathy Study protocol.[14,15] The retinopathy level for a participant was derived by concatenating the levels for the 2 eyes, giving greater weight to the eye with the higher level.[16] This scheme provided a 15-step scale,[17] which, for most analyses, was categorized into 4 groups: 1, no retinopathy; 2, early nonproliferative; 3, moderate to severe nonproliferative; and 4, proliferative.

Retinal microvascular measurements were taken from digitized reproductions of field 1.[14] Computer-assisted measurements of arterioles and venules from a designated area of the fundus were each combined to provide "central equivalents" for the arteriole and venule trunk vessels.[18-20] The central arteriolar and venular equivalents were then expressed as the AVR. An AVR of 1.0 indicates that, on average, retinal arteriole diameters were the same as retinal venule diameters. Smaller values of AVR were thought to represent relative arteriole constriction, although it is possible that at least some venous dilation may play a role in determining the value of the ratio. The distributions of the central retinal artery and vein equivalents and AVR are given in **Table 1**. The mean value for the 2 eyes for 871 persons was used in the analysis. The mean (SD) values in the cohort were as follows: central retinal artery equivalent, 208.1 μm (22.1 μm); central retinal vein equivalent, 246.3 μm (21.9 μm); and AVR, 0.85 (0.07).

Follow-up evaluations of the cohort occurred 4, 10, 14, and 20 years after the baseline evaluation. At each examination, subjects were asked whether a physician had told them that they had had a myocardial infarction, angina, or stroke. The first report of each event was used in our analysis; medical record confirmation of these events was not obtained at the time that they were reported.

Yearly telephone contact with study subjects or a contact person was made to monitor vital status. Local newspapers were monitored for obituaries of study subjects. We obtained death certificates for those known to have died. When we were unable to contact a subject, and the contact persons were unaware of vital status or last known address or death, we submitted the subject's name to the National Death Index. We ascertained that 273 of the 996 participants had died by 2001. There were 27 subjects lost to follow-up, and an additional 101

©2004 American Medical Association. All rights reserved.

Downloaded From: http://archinte.jamanetwork.com/ on 07/21/2017

Table 1. Baseline Risk Factors Considered in Multivariable Models of Cardiovascular Disease (cont)

Risk Factor	Angina			Myocardial Infarction			Stroke		
	No. of Persons	20-y Incidence, %	*P* Value*	No. of Persons	20-y Incidence, %	*P* Value*	No. of Persons	20-y Incidence, %	*P* Value*
Nephropathy									
None	702	14.9	.003	705	11.8	<.001	713	5.3	.95
Proteinuria only	151	21.5		149	23.0		152	6.8	
Dialysis/transplant	21	27.6		22	36.4		21	0.0	
Smoking history									
Never	576	11.5	<.001	576	8.4	<.001	578	3.5	.01
Past	118	34.5		117	26.8		123	7.1	
Current	212	20.1		214	20.8		217	9.3	
Neuropathy									
No	695	11.9	<.001	692	10.6	<.001	697	3.7	<.001
Yes	210	33.2		214	24.0		220	10.7	
Daily aspirin									
No	841	15.3	.02	839	13.4	.95	846	4.2	<.001
Yes	62	28.8		65	13.7		69	18.3	
BMI									
14.4-20.9	231	7.2	<.001	233	6.3	<.001	236	2.8	.03
21.0-23.0	219	15.3		217	9.5		220	5.5	
23.1-25.5	229	15.8		232	13.7		234	4.7	
25.6-50.8	225	27.6		223	24.8		227	8.2	
Retinopathy severity level†									
None	275	6.0	<.001	275	6.0	<.001	275	0.8	<.001
Early nonproliferative	362	17.1		365	12.5		365	3.5	
Moderate to severe nonproliferative	95	26.9		95	21.0		96	13.3	
Proliferative	174	28.5		172	26.9		182	14.7	
CRAE, μm‡									
97.50-198.00	207	20.5	.04	208	17.3	.07	211	7.5	.50
198.05-210.00	203	13.0		205	10.7		206	2.8	
210.04-222.56	203	14.6		204	11.1		206	4.8	
>222.59	201	12.7		201	10.9		204	4.9	
CRVE, μm‡									
152.91-233.10	207	16.0	.98	208	10.1	.13	209	4.5	.13
233.12-246.28	206	14.2		207	12.6		207	2.7	
246.44-260.61	200	13.9		201	10.5		205	6.0	
>260.68	201	16.5		202	16.6		206	6.7	
AVR‡									
0.590-0.808	201	23.0	<.001	203	19.3	<.001	211	9.9	.002
0.809-0.853	204	15.0		206	14.0		205	3.5	
0.854-0.896	204	13.5		205	12.5		205	3.8	
>0.896	205	9.8		204	4.4		206	2.8	

Abbreviations: AVR, arteriovenous ratio; BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); CRAE, central retinal artery equivalent; CRVE, central retinal vein equivalent; DBP, diastolic blood pressure; GHb, glycosylated hemoglobin; SBP, systolic blood pressure.

*Test for trend in all categories except smoking history, when general association χ^2 test was used.

†See "Methods" section for descriptions of retinopathy categories.

‡Values represent quartiles 1 through 4.

who were known to be alive but refused participation in follow-up examinations.

We used death certificate diagnoses for cause of death in our survival analyses. Any mention on the death certificate of diseases of the heart ("any heart") was included as cardiovascular death. The corresponding *International Classification of Diseases, Ninth Revision,* codes were 402, 404, and 410-429, and *International Classification of Diseases, 10th Revision*, codes were I20-I51, with the total number of such deaths being 176.

Characteristics at baseline included in our analysis were age, sex, duration of diabetes, glycosylated hemoglobin level, blood pressure, hypertension, smoking status (never, past, or current), pack-years smoked, presence of neuropathy (a positive response to any or all questions on loss of tactile sensation, numbness or tingling in the hands, and loss of temperature sensitivity), daily aspirin use, body mass index (calculated as weight in kilograms divided by the square of height in meters), nephropathy (none, proteinuria, self-reported dialysis, or transplant), pulse rate, pulse pressure (systolic-diastolic blood pressure in millimeters of mercury), and the retinal vascular characteristics.

DATA HANDLING AND STATISTICS

Analyses were performed with SAS version 8.01 (SAS Institute Inc, Cary, NC).[21] Incidence analyses were performed with the Kaplan-Meier life table approach.[22] Odds ratios for the multivariable models using the angina, myocardial infarction, and stroke end points were computed by means of discrete linear logistic models.[23] Kaplan-Meier survival procedures were used for cardiovascular death.[22] Cox proportional hazards regression was used for the multivariable models.[24] For all analyses, *P* values less than .05 were considered significant, while *P* values of .05 to .10 were considered marginally significant.

©2004 American Medical Association. All rights reserved.

Downloaded From: http://archinte.jamanetwork.com/ on 07/21/2017

Table 2. Multivariable Models for Cardiovascular Disease End Points

	Total No. of Persons	No. of Persons With Event	Risk Factor	OR (95% CI)	*P* Value	Factor *P**
Angina						
A. Excluding ocular characteristics	899	124	Age/10 y	1.8 (1.5-2.1)	<.001	
			Sex, male	0.7 (0.5-1.0)	.04	
			Hypertension (present)	1.9 (1.2-2.9)	.004	
			Neuropathy (present)	2.5 (1.7-3.6)	<.001	
			Past smoking	2.2 (1.4-3.6)	.001	
			Current smoking	1.3 (0.8-2.1)	.21	.005
B. Including diabetic retinopathy	899	124	Retinopathy†/step	1.2 (1.0-1.5)‡	.04	
C. Including AVR	808	107	AVR/quartile§	0.9 (0.7-1.1)‡	.15	
Myocardial infarction						
A. Excluding ocular characteristics	897	101	Age/10 y	1.6 (1.3-1.9)	<.001	
			Sex, male	1.0 (0.7-1.5)	.97	
			DBP/10 mm Hg	1.4 (1.2-1.7)	<.001	
			Neuropathy present	1.7 (1.1-2.6)	.02	
			Pulse pressure, quartile 4 vs all other quartiles§	2.7 (1.7-4.4)	<.001	
			Past smoking	2.4 (1.4-4.2)	.002	
			Current smoking	2.0 (1.2-3.3)	.005	.002
B. Including diabetic retinopathy	897	101	Retinopathy†/step	1.2 (1.0-1.5)‡	.06	
C. Including AVR	811	87	AVR/quartile§	0.8 (0.6-0.9)‡	.01	
Stroke						
A. Excluding ocular characteristics	870	39	Age/10 y	2.0 (1.5-2.6)	<.001	
			Sex, male	2.0 (1.0-3.8)	.05	
			GHb/1%	1.2 (1.1-1.5)	.01	
			Hypertension (present)	2.1 (1.0-4.4)	.04	
			Neuropathy (present)	2.1 (1.0-4.1)	.04	
			Daily aspirin	3.2 (1.5-6.9)	.004	
B. Including diabetic retinopathy	870	39	Retinopathy†/step	1.6 (1.1-2.3)‡	.01	
C. Including AVR	785	34	AVR/quartile§	0.8 (0.6-1.1)‡	.15	

Abbreviations: AVR, arteriovenous ratio; CI, confidence interval; DBP, diastolic blood pressure; GHb, glycosylated hemoglobin; OR, odds ratio.
**P* value for the 3-level smoking variable.
†See "Methods" section for descriptions of retinopathy categories.
‡Odds ratios adjusted for variables in model A of respective end point.
§See Table 1 for quartile ranges.

RESULTS

Of the 996 subjects who were seen at baseline, 918 provided at least an interview at the 4-year follow-up, 815 at the 10-year follow-up, 699 at the 14-year follow-up, and 652 at the 20-year follow-up. With respect to deaths, 64 died before the second examination, 86 more died before the third examination, and 64 more died before the fourth examination. The remainder of the deaths (59) occurred after the fourth examination. In general, those not providing data after baseline tended to be older, had longer duration of diabetes, had hypertension, and were more likely to be male than those returning for follow-up evaluations; glycosylated hemoglobin levels were not different from those of subjects who continued in the study.[25] The prevalence of angina was 3.1%; myocardial infarction, 3.0%; and stroke, 1.0%. Persons with a prevalent condition at baseline were not considered for incidence of that end point. The 20-year age-adjusted cumulative incidence of angina was 18.1%; myocardial infarction, 14.8%; and stroke, 5.9%. Table 1 describes the distributions of characteristics we considered as possible correlates of incidence of the cardiovascular outcomes. Age, duration of diabetes, systolic blood pressure, hypertension, smoking, history of neuropathy, body mass index, pulse pressure, retinopathy, and AVR were significantly related to all end points. Diastolic blood pressure, nephropathy, and daily aspirin use were significant for 2 outcomes. Serum cholesterol levels were not available at the baseline examination.

All significant factors for each outcome were included in developing the multivariable model. A stepwise regression procedure was used to eliminate the nonsignificant factors. When all significant factors except the ocular measures were included in 20-year cumulative incidence multivariable logistic models, the models were similar for myocardial infarction and angina (**Table 2**, model A). For stroke, smoking was not significant, whereas glycosylated hemoglobin and daily aspirin use were significant.

We added ocular factors to the model; first, severity of diabetic retinopathy (Table 2, model B) and, in a separate analysis, AVR (Table 2, model C). This was done because the Spearman rank correlation coefficient between AVR and severity of retinopathy (full scale) was −0.46 ($P<.001$). In these multivariable models, the severity of retinopathy was associated with increased odds of all 3 cardiovascular disease outcomes, but was of borderline significance for myocardial infarction. Lower AVR was associated with increased odds of all the outcomes, but was significant only for myocardial infarction.

Survival plots by severity of any retinopathy (**Figure 1**) indicated that more severe retinopathy was

©2004 American Medical Association. All rights reserved.

Downloaded From: http://archinte.jamanetwork.com/ on 07/21/2017

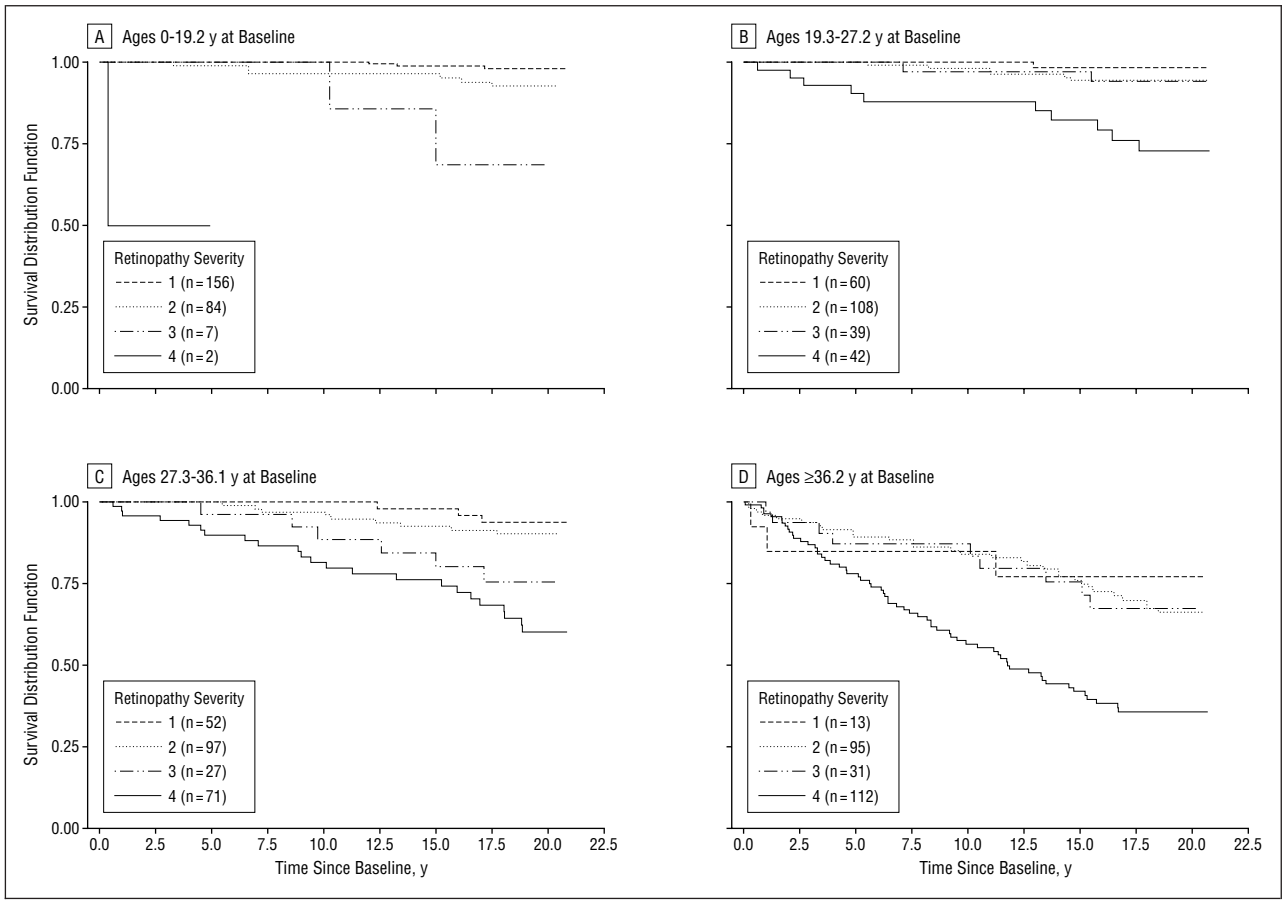

Figure 1. Survival by severity of diabetic retinopathy in 4 age groups. See the "Methods" section for description of retinopathy categories. Numbers in the figure key represent the number at risk at baseline.

associated with greater mortality in all age groups. This was most apparent when stratum 4 (proliferative retinopathy) was compared with the other groups. Survival plots by quartile of AVR suggested that it was not related to mortality except in the oldest age group, when those with the smallest AVR had the poorest survival experience (**Figure 2**).

Multivariable analyses were performed for mortality involving heart disease (any heart) including significant systemic variables first, before ocular characteristics were added (**Table 3**, model A). We did not consider nephropathy in this first analysis because of the possible confounding of the retinal vascular characteristics–heart disease mortality relationship by nephropathy. The significant factors were age, sex, duration of diabetes, glycosylated hemoglobin level, diastolic blood pressure (per 10 mm Hg), neuropathy, hypertension, and history of cardiovascular disease; smoking was of borderline significance. When category of severity of retinopathy was included, there was a significant trend of increased risk with increasing severity ($P=.004$) (Table 3, model B). When quartile of AVR was added to the model instead of severity of retinopathy, there was a significant trend of increased risk with decreased AVR ($P=.01$) (Table 3, model C). If renal insufficiency was included as a variable instead of the severity of the ocular variables, it increased mortality risk significantly ($P<.001$) (data not shown).

COMMENT

Our data are consistent with the possibility that microvascular characteristics in those with type 1 diabetes mellitus precede macrovascular disease, as reflected by cardiovascular disease and mortality involving heart disease. The severity of diabetic retinopathy appeared to be more consistently related to the outcomes we examined than did AVR. Diabetic retinopathy and AVR were highly correlated and may be variant manifestations of the same process. Both were related to duration of diabetes, blood pressure, and diabetic nephropathy.[14,25] In those without diabetes, AVR, as well as retinal blot hemorrhages and microaneurysms, were associated with blood pressure,[7,9] so our findings in those with diabetes were not novel. It may be that the hyperglycemia of diabetes was another insult to the retina or it exacerbated effects of blood pressure, resulting in hemorrhages, microaneurysms, and more severe lesions of retinopathy; this may also have affected AVR–blood pressure relationships. In those without diabetes in the Atherosclerosis Risk in Communities Study,[7-10,26] AVR and (nondiabetic) retinopathy were related to cardiovascular events. Wong et al[8] found that AVR was associated with coronary heart disease in women, but not in men, in the Atherosclerosis Risk in Communities Study. In our population, we found

©2004 American Medical Association. All rights reserved.

Downloaded From: http://archinte.jamanetwork.com/ on 07/21/2017

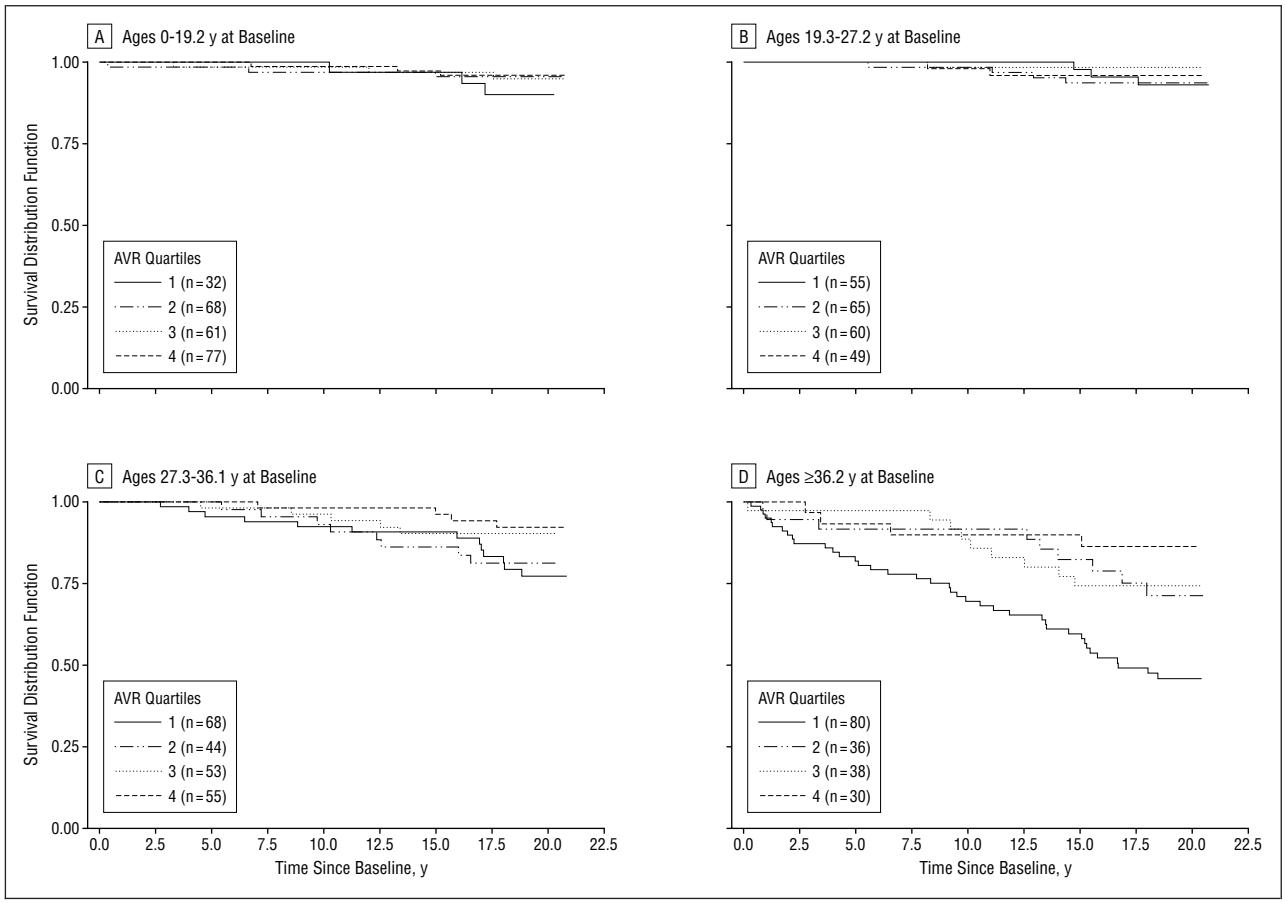

Figure 2. Survival by quartile ranges of arteriovenous ratio (AVR) in 4 age groups. Arteriovenous ratio categories were as follows: quartile 1, 0.590 to 0.808; quartile 2, 0.809 to 0.853; quartile 3, 0.854 to 0.896; and quartile 4, greater than 0.896. Numbers in the figure key represent the number at risk at baseline.

Table 3. Multivariable Models for Mortality From Any Heart

	Total No. of Persons	No. of Persons With Event	Risk Factor	HR (95% CI)	*P* Value
A. Excluding ocular characteristics	934	162	Age/10 y	1.4 (1.2-1.7)	<.001
			Sex, male vs female	1.6 (1.2-2.2)	.005
			Duration/10 y	1.5 (1.2-1.9)	<.001
			GHb/1%	1.2 (1.1-1.3)	<.001
			DBP/10 mm Hg	1.3 (1.1-1.5)	.002
			Neuropathy	1.9 (1.4-2.6)	<.001
			Hypertension	2.6 (1.8-3.9)	<.001
			Smoking/10 pack-years	1.1 (1.0-1.1)	.09
			History of CVD	3.0 (1.9-4.6)	<.001
B. Including diabetic retinopathy	934	162	Retinopathy*/step	1.3 (1.1-1.5)†	.004
C. Including AVR	832	104	AVR/quartile	0.8 (0.6-0.9)†	.01

Abbreviations: AVR, arteriovenous ratio; CI, confidence interval; CVD, cardiovascular disease; DBP, diastolic blood pressure; GHb, glycosylated hemoglobin; HR, hazard ratio.

*See "Methods" section for descriptions of retinopathy categories.

†Adjusted for variables in model A.

no difference in the relationships of the retinal vascular characteristics to outcomes by sex. The reasons for this are not apparent.

The population enrolled in our study had risk factors for incident cardiovascular events and mortality from heart disease that were similar to those found in other population-based studies of persons with diabetes (eg, age, blood pressure, smoking, and duration of diabetes).[27-32] In the univariable and multivariable models, glycosylated hemoglobin was not significantly associated with angina and myocardial infarction. The Pittsburgh Epidemiology of Diabetes Complications Study also found no significant relationship between glycemia and coronary disease.[32] In our analysis, the level of glycemia in those with diabetes was significantly associated with incidence of stroke. Despite the relative infrequency of stroke, the confidence limits were

©2004 American Medical Association. All rights reserved.

Downloaded From: http://archinte.jamanetwork.com/ on 07/21/2017

not wide (odds ratio, 1.2; 95% confidence interval, 1.01-1.50). Diabetes has previously been shown to increase the risk of stroke,[33-36] but we are unaware of any previous study that has found the risk in people with diabetes to be related to level of glycemia.

Self-reported symptoms of sensory neuropathy were significantly associated with all 3 cardiovascular events and mortality. We chose to include this variable as a possible risk factor for 2 reasons. One is that it is common; its prevalence tends to increase with age[37] and duration of diabetes[37,38] in those with type 2 diabetes mellitus, and it may serve as a marker of general complications in diabetes. The other is that we use it as a surrogate for autonomic neuropathy, which may influence our cardiovascular disease end points.

We chose to use "any mention" of heart disease on the death certificate in our survival analyses because a cardiac event is often the terminal event in people who, in addition, have other life-threatening complications of diabetes. The heart disease codes we included reflect atherosclerotic heart disease. Although one may be concerned about possible heterogeneity resulting from our use of several *International Classification of Diseases* codes, we have found that even when using a broader classification of "all causes [of death]," the risk factors were very similar to those for our grouping of heart disease causes.[39] While we cannot be certain that our grouping of causes of death does not obscure a more specific relationship of the microvascular characteristics to specific heart disease mortality codes, our sample would be too small to detect an effect in a subgroup of heart disease classification with great confidence.

We did not consider nephropathy in our early models of risk factors for mortality because that complication is highly correlated with retinopathy and may be a manifestation of the same process that causes retinopathy. When the nephropathy was considered in addition to retinopathy, nephropathy was significant and retinopathy no longer was significant. This is in keeping with findings of other studies that have found that nephropathy in diabetes increases the risk of ischemic heart disease mortality and morbidity.[40-42] It is likely that nephropathy not only is a direct result of diabetic microangiopathy but that, when present, it is associated with elevation in fibrinogen level, blood viscosity, lipoprotein level, and platelet aggregation,[4,43-45] which may increase risk of death. Incidence of all 3 end points was higher in those who took aspirin daily. This was most remarkable for stroke. While this could be due to a causal association, it may instead reflect the clinician's recommendation to subjects who they thought were sicker and were, therefore, at greater risk for stroke. We do not have enough stroke events to evaluate whether the aspirin association is related to an especially high risk of hemorrhagic stroke.

Limitations of our study include the fact that self-report may be inaccurate, leading to underreporting or overreporting. Queries were done at study examinations that were about 5 years apart, and these relatively long intervals may have led to faulty memory of study subjects. It is not clear whether these sorts of errors would be likely to lead to overestimates or underestimates, or whether they were likely to bias our estimates of the relationships of cardiovascular events to microvascular characteristics. Medical records do not always solve the problem because they are not always complete or accurate as a result of transcription errors and incomplete copying of records at the institutions. Another consideration is that this cohort was defined 20 years ago. Interim changes in patterns of care, which have occurred relatively recently, were likely to influence cardiovascular disease and mortality and possibly the relationship of microvascular characteristics to these outcomes. Cohorts defined more recently and followed up more frequently with more precise documentation of cardiovascular disease and its risk factors will afford better opportunities to evaluate the associations of microvascular characteristics to these end points.

In conclusion, we found that age-adjusted cumulative incidence of cardiovascular disease was high in this cohort of persons with type 1 diabetes mellitus, and that these end points were associated with retinal microvascular characteristics 20 years earlier. The pathways linking the microvascular to macrovascular characteristics require further research.

Accepted for publication October 3, 2003.

This study was supported by grant HL59259 from the National Institutes of Health, Bethesda, Md.

Correspondence: Barbara E. K. Klein, MD, Department of Ophthalmology and Visual Sciences, University of Wisconsin–Madison, 610 N Walnut St, 409 WARF, Madison, WI 53726.

REFERENCES

1. Wilson PW, Cupples LA, Kannel WB. Is hyperglycemia associated with cardiovascular disease? the Framingham Study. *Am Heart J.* 1991;121(2, pt 1):586-590.
2. Laws A, Marcus EB, Grove JS, Curb JD. Lipids and lipoproteins as risk factors for coronary heart disease in men with abnormal glucose tolerance: the Honolulu Heart Program. *J Intern Med.* 1993;234:471-478.
3. Manson JE, Colditz GA, Stampfer MJ, et al. A prospective study of maturity-onset diabetes mellitus and risk of coronary heart disease and stroke in women. *Arch Intern Med.* 1991;151:1141-1147.
4. Seeman T, Mendes de Leon C, Berkman L, Ostfeld A. Risk factors for coronary heart disease among older men and women: a prospective study of community-dwelling elderly. *Am J Epidemiol.* 1993;138:1037-1049.
5. Stamler J, Vaccaro O, Neaton JD, Wentworth D. Diabetes, other risk factors and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. *Diabetes Care.* 1993;16:434-444.
6. Yodaiken RE. The relationship between diabetic capillaropathy and myocardial infarction: a hypothesis. *Diabetes.* 1976;25:928-930.
7. Wong TY, Klein R, Couper DJ, et al. Retinal microvascular abnormalities and incident stroke: the Atherosclerosis Risk in Communities Study. *Lancet.* 2001; 358:1134-1140.
8. Wong TY, Klein R, Sharrett AR, et al. Retinal arteriolar narrowing and risk of coronary heart disease in men and women: the Atherosclerosis Risk in Communities Study. *JAMA.* 2002;287:1153-1159.
9. Sharrett AR, Hubbard LD, Cooper LS, et al. Retinal arteriolar diameters and elevated blood pressure: the Atherosclerosis Risk in Communities Study. *Am J Epidemiol.* 1999;150:263-270.
10. Wong TY, Klein R, Sharrett AR, et al. Cerebral white matter lesions, retinopathy, and incident clinical stroke. *JAMA.* 2002;288:67-74.
11. Klein R, Klein BEK, Moss SE, DeMets DL, Kaufman I, Voss PS. Prevalence of diabetes mellitus in southern Wisconsin. *Am J Epidemiol.* 1984;119:54-61.
12. Klein R, Moss SE, Klein BEK, Davis MD, DeMets DL. The Wisconsin Epidemiologic Study of Diabetic Retinopathy, XII: relationship of C-peptide and diabetic retinopathy. *Diabetes.* 1990;39:1445-1450.

©2004 American Medical Association. All rights reserved.

Downloaded From: http://archinte.jamanetwork.com/ on 07/21/2017

13. Moss SE, Klein R, Klein BE, Spennetta TL, Shrago ES. Methodologic considerations in measuring glycosylated hemoglobin in epidemiologic studies. *J Clin Epidemiol.* 1988;41:645-649.
14. Klein R, Klein BEK, Moss SE, Davis MD, DeMets DL. The Wisconsin Epidemiologic Study of Diabetic Retinopathy, II: prevalence and risk of diabetic retinopathy when age at diagnosis is less than 30 years. *Arch Ophthalmol.* 1984;102:520-526.
15. *Early Treatment Diabetic Retinopathy Study (ETDRS): Manual of Operations.* Springfield, Va: US Dept of Commerce; 1985:18-1–18-8. NTIS publication PB85-223006.
16. Klein BE, Davis MD, Segal P, et al. Diabetic retinopathy: assessment of severity and progression. *Ophthalmology.* 1984;91:10-17.
17. Klein R, Klein BE, Moss SE, Cruickshanks KJ. The Wisconsin Epidemiologic Study of Diabetic Retinopathy, XIV: ten-year incidence and progression of diabetic retinopathy. *Arch Ophthalmol.* 1994;112:1217-1228.
18. Parr JC, Spears GF. General caliber of the retinal arteries expressed as the equivalent width of the central retinal artery. *Am J Ophthalmol.* 1974;77:472-477.
19. Parr JC, Spears GF. Mathematic relationships between the width of a retinal artery and the widths of its branches. *Am J Ophthalmol.* 1974;77:478-483.
20. Hubbard LD, Brothers RJ, King WN, et al. Methods for evaluation of retinal microvascular abnormalities associated with hypertension/sclerosis in the Atherosclerosis Risk in Communities Study. *Ophthalmology.* 1999;106:2269-2280.
21. SAS Institute Inc. *SAS/STAT User's Guide*, *Version 8.* Cary, NC: SAS Institute Inc; 1999.
22. Fleiss JL. *Statistical Methods for Rates and Proportions.* New York, NY: John Wiley & Sons Inc; 1973.
23. Hosmer DW, Lemeshow S. *Applied Logistic Regression.* New York, NY: John Wiley & Sons Inc; 1989.
24. Meier P. Anatomy and interpretation of the Cox regression model. *ASAIO J.* 1985; 8:3-12.
25. Klein R, Klein BE, Moss SE, et al. Retinal vascular abnormalities in persons with type 1 diabetes: the Wisconsin Epidemiologic Study of Diabetic Retinopathy: XVIII. *Ophthalmology.* 2003;110:2118-2125.
26. Wong TY, Klein R, Klein BE, Tielsch JM, Hubbard L, Nieto FJ. Retinal microvascular abnormalities and their relationship with hypertension, cardiovascular disease, and mortality. *Surv Ophthalmol.* 2001;46:59-80.
27. Qureshi AI, Giles WH, Croft JB. Impaired glucose tolerance and the likelihood of nonfatal stroke and myocardial infarction: the Third National Health and Nutrition Examination Survey. *Stroke.* 1998;29:1329-1332.
28. Gerson MC, Khoury JC, Hertzberg VS, Fischer EE, Scott RC. Prediction of coronary artery disease in a population of insulin-requiring diabetic patients: results of an 8-year follow-up study. *Am Heart J.* 1988;116:820-826.
29. 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.* 1997;157:1413-1418.
30. Knuiman MW, Welborn TA, McCann VJ, Stanton KG, Constable IJ. Prevalence of diabetic complications in relation to risk factors. *Diabetes.* 1986;35:1332-1339.
31. American Diabetes Association. Role of cardiovascular risk factors in prevention and treatment of macrovascular disease in diabetes. *Diabetes Care.* 1989; 12:573-579.
32. Orchard TJ. From diagnosis and classification to complications and therapy: DCCT, part II: Diabetes Control and Complications Trial. *Diabetes Care.* 1994;17:326-328.
33. Barrett-Connor E, Khaw KT. Diabetes mellitus: an independent risk factor for stroke? *Am J Epidemiol.* 1988;128:116-123.
34. Kittner SJ, White LR, Losonczy KG, Wolf PA, Hebel JR. Black-white differences in stroke incidence in a national sample: the contribution of hypertension and diabetes mellitus. *JAMA.* 1990;264:1267-1270.
35. Abbott RD, Donahue RP, MacMahon SW, Reed DM, Yano K. Diabetes and the risk of stroke: the Honolulu Heart Program. *JAMA.* 1987;257:949-952.
36. Wolf PA, D'Agostino RB, Belanger AJ, Kannel WB. Probability of stroke: a risk profile from the Framingham Study. *Stroke.* 1991;22:312-318.
37. Franklin GM, Kahn LB, Baxter J, Marshall JA, Hamman RF. Sensory neuropathy in non–insulin-dependent diabetes mellitus: the San Luis Valley Diabetes Study. *Am J Epidemiol.* 1990;131:633-643.
38. Harris M, Eastman R, Cowie C. Symptoms of neuropathy in adults with NIDDM in the US population. *Diabetes Care.* 1993;16:1446-1452.
39. Moss SE, Klein R, Klein BE, Meuer SM. The association of glycemia and cause-specific mortality in a diabetic population. *Arch Intern Med.* 1994;154:2473-2479.
40. Morrish NJ, Stevens LK, Fuller JH, Jarrett RJ, Keen H. Risk factors for macrovascular disease in diabetes mellitus: the London follow-up to the WHO Multinational Study of Vascular Disease in Diabetics. *Diabetologia.* 1991;34:590-594.
41. Warram JH, Laffel LM, Ganda OP, Christlieb AR. Coronary artery disease is the major determinant of excess mortality in patients with insulin-dependent diabetes mellitus and persistent proteinuria. *J Am Soc Nephrol.* 1992;3(4, suppl): S104-S110.
42. Borch-Johnsen K, Kreiner S. Proteinuria: value as predictor of cardiovascular mortality in insulin dependent diabetes mellitus. *BMJ.* 1987;294:1651-1654.
43. Vukovich TC, Schernthaner G, Knobi PN, Hay U. The effect of near-normoglycemic control on plasma factor VIII/von Willebrand factor and fibrin degradation products in insulin-dependent diabetic patients. *J Clin Endocrinol Metab.* 1989;69:84-89.
44. Vane JR, Anggard EE, Botting RM. Regulatory functions of the vascular endothelium. *N Engl J Med.* 1990;323:27-36.
45. Jensen T, Bjerre-Knudsen J, Feldt-Rasmussen B, Deckert T. Features of endothelial dysfunction in early diabetic nephropathy. *Lancet.* 1989;1:461-463.

©2004 American Medical Association. All rights reserved.

Downloaded From: http://archinte.jamanetwork.com/ on 07/21/2017