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The 25-year Incidence of Visual Impairment in Type 1 Diabetes Mellitus: The Wisconsin Epidemiologic Study of Diabetic Retinopathy

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Abstract

Objective—To examine the 25-year cumulative incidence of visual impairment (VI) and its relation to various risk factors.

Design—Population-based study.

Participants—Nine hundred and fifty-five insulin-taking persons living in an 11-county area in southern Wisconsin with type 1 diabetes diagnosed before age 30 years who participated in a baseline (1980–1982) and at least one of 4 follow-up (4-, 10-, 14-, and 25-year) examinations or died before the first follow-up examination (n=64).

Methods—Best corrected visual acuity (VA) was measured using a modification of the Early Treatment Diabetic Retinopathy Study protocol. VI and severe VI were defined as best corrected VA in the better eye of 20/40 or worse and 20/200 or worse, respectively.

Main Outcome Measure—Incidence of VI.

Results—The 25-year cumulative incidences of VI and severe VI (accounting for competing risk of death) were 13% and 3%, respectively. Multivariate models showed increased risk of VI was associated (Hazard Ratio, 95% Confidence Interval, and *P*-value) with more severe baseline retinopathy (1.14 per 1 step increase in retinopathy level, 1.03 to 1.27, *P* < 0.01), presence of cataract (2.49, 1.53 to 4.04, *P* < .001), higher glycosylated hemoglobin (1.28 per 1%, 1.16 to 1.42, *P* < 0.001), presence of hypertension (1.72, 1.05 to 2.83, *P* = 0.03), and currently smoking (vs. never smoked, 1.63, 1.01 to 2.61, *P* = 0.04) but not proteinuria.

Conclusions—These data show that the 25-year cumulative incidence of VI is related to modifiable risk factors and, therefore, that VI might be reduced by better glycemic and blood pressure control and avoidance of smoking.

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Diabetic retinopathy (DR) is an important cause of visual impairment (VI), especially in persons 25–65 years of age.^{1–4} While epidemiological studies have described the incidence of VI and its relationships to various risk factors, many of these studies have been in persons with type 2 diabetes and few have examined these relationships over a long period of time.^{5–14} In this report, we extend our previous observations by describing the 25-year cumulative incidence of any and severe VI and the doubling of the visual angle in a large cohort of persons with type 1 diabetes mellitus (T1DM) participating in the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR).^{5,7,11}

METHODS

Case identification methods and descriptions of the population have appeared in previous reports.^{5,7,11,15–21} Briefly, the study area consisted of 11 counties in southern Wisconsin. From July 1, 1979 to June 30, 1980, 10135 persons with diabetes were identified in the practices of 452 of 457 primary care physicians in the area. A two part sample of 2990 of these persons was invited to participate in the baseline examination from 1980 to 1982. The first part consisted of the entire population of persons taking insulin who were diagnosed as having diabetes before 30 years of age ($n = 1210$), and the second part consisted of a probability sample of persons who were diagnosed as having diabetes at or after 30 years of age ($n = 1780$).^{15–22} Based on C-peptide testing, the first group is referred to as T1DM and analyses are limited to this group. Surviving younger onset persons were invited to participate in follow up examinations in 1984–86, 1990–92, 1995–96, 2000–2002, and 2005–2007.^{17–21} Differences in baseline characteristics among those who participated in a follow-up examination and those who did not have been presented elsewhere.^{17–21}

All examinations followed a similar protocol, which was approved by the institutional Human Subjects Committee of the University of Wisconsin and conformed to the tenets of the Declaration of Helsinki. The pertinent parts of the examination consisted of obtaining informed signed consent measuring blood pressure,²³ measuring refractive error and best corrected visual acuity (VA) for distance using a modified Early Treatment Diabetic Retinopathy Study (ETDRS) protocol in which the charts were reduced in size for a 2-meter distance,²⁴ dilating the pupils, administering a medical history questionnaire, performing a slit lamp examination, performing an ophthalmoscopic examination, taking stereoscopic color fundus photographs of seven standard fields,²⁵ determining urine protein level, and determining blood glucose and glycosylated hemoglobin (HbA1c) levels. Because the 2000–2002 examination was primarily focused on cardiovascular disease, measurements of refractive error, VA, dilation of pupils, and fundus photography were not completed at this examination.

For each eye, the best corrected VA was recorded as the number of letters read correctly from 0 (20/250) to 70 (20/10).¹⁶ For eyes with VA worse than 20/250, one of six levels of VA was recorded: 20/320, 20/400, 20/800, hand motions, light perception, and no light perception. The participants' VA was defined as the VA in the better eye. In this study, we define severe VI as a VA of 20/200 or less in the better eye. Any VI is defined as a VA of 20/40 or less in the better eye. A doubling of the visual angle is defined as a loss of 15 letters (i.e., a change from 55 to 40 letters corresponds to a visual acuity change from 20/20 to 20/40). Persons with a VA of no light perception at baseline were not at risk for doubling of the visual angle. For analyses with demographic and systemic factors, this was determined for the better eye. For analyses with ocular factors, right and left eyes were analyzed separately.

To determine the severity of retinopathy in each eye, all fundus photographs were graded using a modification of the ETDRS classification scheme.^{18,25} Briefly, level 10 represents no retinopathy, levels 21 through 53 represent nonproliferative retinopathy of increasing severity, and levels 60 through 85 represent proliferative retinopathy of increasing severity. Macular

edema was also determined from the fundus photographs as described previously.²⁶ Macular edema was considered present if any area of the retina within 1 disc diameter from the center of the macula was thickened or if there was a prior history of macular edema with evidence of photocoagulation treatment consistent with it. Panretinal and or focal/grid photocoagulation was determined by grading of fundus photographs. Cataract status (cortical, nuclear, and posterior subcapsular) was ascertained at the slit lamp. Glaucoma was based on history of glaucoma and treatment with intraocular pressure lowering medications.

Current age was defined as the age at the time of the baseline examination. Duration of younger onset diabetes was the time interval between diagnosis of diabetes and the specific examination. Age at diagnosis was obtained from physician's chart. Glycemic control was measured by HbA1c using a microcolumn technique.^{27,28} Hypertension was defined as a mean systolic blood pressure ≥ 160 mmHg and/or a mean diastolic blood pressure ≥ 95 mmHg or a history of antihypertensive medication at the time of examination in individuals ≥ 25 years of age or a mean systolic blood pressure of ≥ 140 mmHg and/or a mean diastolic blood pressure of ≥ 90 mmHg, and/or a history of antihypertensive medication at the time of examination in younger persons. Urine samples were collected and tested for gross proteinuria by means of a reagent strip (Labstix, Ames, Elkhart, IN). Urine protein was defined as absent (< 0.30 g/l) or present (≥ 0.30 g/l). A subject was classified as a nonsmoker if he/she had smoked fewer than 100 cigarettes in his/her lifetime, a former smoker if he/she had smoked more than this number but had stopped smoking before the baseline examination, and as a current smoker if he/she had not stopped. Pack-years smoked was defined as the number of packs of cigarettes (20 cigarettes/pack) smoked daily times the number of years smoked.

Statistics

SAS version 9 was used for analyzing the data (SAS Institute Inc., Cary, NC). Data were structured such that each participant contributed data for every examination VA was measured until they obtained the VI outcome or were otherwise censored. Cumulative 25-year incidence of visual impairment and of doubling of the visual angle were calculated considering competing risk of death.²⁹ This is an adaptation of the Kaplan-Meier product limit method that only considers those that were alive and free of disease to be at risk for failure rather than the traditional approach that treats those censored because of death as still being at risk for failure. In the competing event approach, both death and the event of interest are included in calculating the probability of surviving up to time t . There were a total of 367 subjects who died (195 of these are considered competing events), 64 (42 competing) from the baseline examination to the start of the first follow-up, 86 (48) from the first follow-up examination to the start of the second follow-up, 64 (29) from the second follow-up examination to the start of the third follow-up examination, and 153 (76) from the third follow-up examination to the start of the fifth follow-up examination. Estimated incidence and rates of progression between examinations were converted to average annual rates using the formula: $1 - (1 - p_n)^{1/n}$, where n is the number of years between examinations and p_n is the cumulative rate between examinations.

For multivariable analyses, we used generalized linear models for the binary outcomes (incidence of VI and doubling of the visual angle during the examination interval) using the complementary log-log link function to estimate underlying continuous-time proportional hazard models while accounting for the varying follow-up times between examinations. For these analyses, duration of diabetes was the time variable and the baseline hazard was assumed to be piecewise constant within 5-year bands of diabetes duration starting at 20 years and continuing to > 40 years. Hazard ratios estimates were calculated by exponentiation of estimated coefficients. PROC NLMIXED of SAS version 9.1 (Cary, NC) was used for these analyses. Three sets of models were considered: 1) models including only baseline

characteristics; 2) models including baseline characteristics without retinopathy severity included; and 3) models using time-varying covariates updated at each follow-up examination (i.e., for each time interval in which a subject participated, the values of the risk factors at the beginning of the interval were used).³⁰

RESULTS

Nine hundred and ninety-five participants contributed 3719 participant-visits for the analysis of the incidence of VI. Characteristics of the cohort have been described in detail elsewhere.^{5,7,11,15–21} For the 482 participants in the 2005–2007 examination, the baseline values of characteristics were: mean age 24.9 ± 9.3 years, mean duration of diabetes 10.7 ± 7.1 years, mean HbA1c $10.5 \pm 2.0\%$, mean systolic and diastolic blood pressures 118.4 ± 14.0 and 77.0 ± 10.6 mmHg, respectively, mean body mass index 23.1 ± 3.8 kg/m², and the mean pack-years smoked (among those 18 years of age and older, (n=369)) was 4.0 ± 10.0 . At baseline, 49.8% of the cohort was male, 12.3% had a history of hypertension, 12.3% had proteinuria, 24.1% (of those 18 years of age and older) were current smokers, 2.3% were visually impaired of whom 9% were severely impaired, 14.0% had a cataract, 0.8% had glaucoma, 8.3% had proliferative DR, 5.3% had macular edema of whom 60% had clinically significant macular edema, 5.2% had panretinal photocoagulation treatment, and 0.2% had focal or grid photocoagulation treatment for macular edema.

The mean decrease in the number of letters read correctly over the 25-year period of the study was similar in the right (-6.7 ± 18.9) and left eyes (-7.6 ± 18.0 , $P = 0.46$). Those who had shorter duration of diabetes lost fewer letters during the 25-year period than those who had longer duration of diabetes at baseline (Figure 1) but this trend was not statistically significant. For right eyes, it varied from -3.87 letters ± 17.0 in people with < 5 years duration of diabetes to -9.29 ± 24.6 in people with 15 or more years of diabetes at baseline. Similar relations were found for left eyes (data not shown). There was a statistically significant inverse relationship between the mean change in the number of letters read correctly between examinations and severity of DR such that those with no DR at baseline lost fewer letters during the 25-year period than those with more severe retinopathy (Figure 2). The mean decrease in the number of letters read correctly varied from -4.6 letters ± 16.3 in right eyes with no DR at baseline to -20.5 ± 42.1 in right eyes with proliferative DR present at baseline. Similar relations were found for left eyes (data not shown).

Factors Associated with the Cumulative Incidence of Visual Impairment

The 25-year cumulative incidence of any VI and severe VI in the worse eye in the population accounting for the competing risk of death was 13% (95% Confidence Interval [CI] 11 to 16%) and 3% (95% CI 1 to 4%), respectively (Table 1). For right eyes, the 25-year cumulative incidence of any VI and severe VI in the population was 22% (95% CI 19 to 25%) and 6% (95% CI 4 to 7%), respectively, while for left eyes, it was 21% (95% CI 18 to 24%) and 6% (95% CI 4 to 8%), respectively. Using the World Health Organization definitions, the 25-year cumulative incidence of moderately severe visual impairment (best corrected visual acuity in the better eye of $\leq 20/80$ and $> 20/200$) and “blindness” (best corrected visual acuity in the better eye of $< 20/400$) was 3.0% and 1.2%, respectively.

Cumulative incidence of VI and severe VI in the better eye and competing risk of death increased with age and duration of diabetes (Table 1). The estimates of the annual incidence of any and severe VI over the four study intervals are presented in Figure 3. Because the length of the interval varies over the study, the width of the bars in the figure reflects the length of the interval. The annualized estimates are similar for any VI except for the last period where it was markedly lower; a less consistent temporal pattern was found for severe VI. To evaluate whether this drop in the last period is real or due to the different interval length, we examined

at the annualized incidence between the 1980–82 and 1990–92 examinations. This annualized rate of 0.65 (not shown) for any VI is still higher than the comparable interval 1994–96 to 2005–2007 annualized rate of 0.28.

In univariate analyses, having a higher HbA1 level, higher systolic or diastolic blood pressure, hypertension, gross proteinuria, being a current smoker, having more pack-years smoked while having diabetes, having more severe DR, having cataract, and having macular edema at baseline were significantly associated with the incidence of any VI (Table 2). Being male, having glaucoma or having a greater BMI was not associated with the incidence of VI (Table 2). Similar analyses were not done for severe VI due to its low incidence.

Multivariate analyses showed that while controlling for duration of diabetes, increased risk of VI was associated with more severe baseline DR, cataract presence, higher HbA1, presence of hypertension, and currently smoking (vs. never smoked) (Table 2) but not proteinuria, a history of glaucoma, or macular edema (data not shown). When DR severity was not entered into the model, presence of gross proteinuria at baseline (Hazard Ratio [HR] 1.74, 95% CI 1.07 to 2.84; $P = 0.03$) was significantly associated and macular edema (HR 1.67, 95% CI 0.97 to 2.88; $P = 0.07$) was marginally associated with the incidence of VI.

Time-varying covariate analyses were consistent with analyses using only baseline measurements with retinopathy in the model except that the associations of proteinuria with incident VI was statistically significant (HR 1.80, 95% CI 1.14 to 2.84; $P = 0.01$), while hypertension and smoking status with incident VI were no longer statistically significant (data not shown).

Among the 160 right eyes that developed any VI, 75% had proliferative diabetic retinopathy, 17% had clinically significant macular edema, 13% had glaucoma and 55% had cataract at a previous examination or at the examination that the VI had been first detected. Similar findings were found in left eyes (data not shown).

Factors Associated with the Cumulative Incidence of Doubling of the Visual Angle

The 25-year cumulative incidence of doubling of the visual angle in the population accounting for the competing risk of death was 15% (95% CI 13 to 18%, Table 1). Cumulative incidence of doubling of the visual angle increased with age and duration of diabetes (Table 1).

In univariate analyses, higher HbA1 level, higher systolic or diastolic blood pressure, hypertension, gross proteinuria, having more pack-years smoked, having more severe DR, having cataract, having a history of glaucoma, and having macular edema at baseline were significantly associated with the incidence of doubling of the visual angle (Table 3). Being male or having greater body mass index was not associated with incidence of doubling of the visual angle (Table 3).

Multivariate analyses showed that while controlling for duration of diabetes, increased risk of doubling of the visual angle was associated with cataract presence, history of glaucoma, higher HbA1, and proteinuria (Table 3). There were borderline associations with more severe baseline retinopathy and current smoking (vs. never smoked) (Table 3) but not hypertension or macular edema (data not shown). When DR severity was not entered into the model, there was a borderline association between presence of hypertension (HR 1.53, 95% CI 0.96 to 2.43; $P = 0.07$) with the incidence of doubling of the visual angle.

Time-varying covariate analyses were consistent with analyses using only baseline measurements with retinopathy in the model except that the association of macular edema with incident VI was of borderline statistical significance (HR 1.52, 95% CI 1.00 to 2.31; $P = 0.054$),

while history of glaucoma with incident VI was no longer statistically significant (data not shown).

DISCUSSION

The data reported herein provide unique population-based information regarding the 25-year cumulative rates of VI and change in vision and their relationships to retinopathy severity, cataract, glycemia, blood pressure, smoking, and other factors in persons with T1DM. The overall 25-year incidence of any VI (13%), and doubling of the visual angle (15%) were high and the strongest most consistent relationships were with glycemia, retinopathy severity, cataract, and smoking.

There are few other population-based cohorts of persons with T1DM with a similar period of follow-up to which these data can be compared. One is the 25 year follow-up of persons with T1DM living in Fyn County, Denmark (Invest Ophthalmol Vis Sci 2008;49:E-abstract 1161). They report a 25-year incidence of severe VI of 7.5% which is higher than the 3% found in the WESDR cohort. The higher incidence in the Danish cohort may be due to the identification of their subjects with incident severe VI through blindness registries, while in the WESDR, incident severe VI was identified only at the time of each follow-up examination. It is possible that WESDR subjects with incident severe VI, who are at a higher risk of death, were less likely to be identified if they died before coming in for a follow-up examination. In addition, cumulative incidence taking into account competing risk of death are reported in the WESDR while in the Fyn County study, severe VI did not take competing risk of death into account. In a 20 year follow-up of a cohort diagnosed to have diabetes in Rochester, Minnesota, from 1945 to 1969, the cumulative incidence of severe VI was 8.2%.³¹ However, the incidence of severe VI was not reported by type of diabetes in that study. Most other studies have reported severe VI in persons with T1DM over shorter periods of time.^{6,8,32} Comparisons of visual loss among studies must be made with care due to differences in the methods used to ascertain visual loss and the periods in time in which the cohorts were studied.

Based on our findings, we estimate that over a 25-year study period, of the 515,000 to 1.3 million Americans thought at present to have T1DM, that approximately 66,950 to 169,000 will develop VI, of whom 15,400 to 39,000 will develop severe VI (NIDDK Clearing House <http://www.medhelp.org/NIHlib/GF-254.html#four> accessed December 26, 2008). The decline in annualized incidence of VI between the 1994–95 and 2005–06 examinations from earlier periods suggest the possibility that applying these figures to persons who currently have T1DM may overestimate the number of persons who will develop VI over the next 25 years. This information on declining incidence of VI is important in planning for counseling and rehabilitative services, projecting costs, measuring temporal trends, developing causal inferences, and providing sample size estimates for conducting clinical trials. For example, if there is a “true” decrease in the incidence of VI in persons with T1DM, there may be a need for fewer health care resources to support and rehabilitate these individuals.

Visual impairment was strongly associated with the severity of retinopathy and presence of macular edema at baseline. Compared to persons without DR at baseline, persons with proliferative DR had an 8 fold higher risk of developing VI and a 29 fold higher risk of developing severe VI over the 25-year period (Klein R, unpublished data). Using time-varying covariates showed the risk of incident VI when proliferative DR or macular edema was present appeared to be similar in each period despite the fact that a higher proportion of eyes with proliferative DR and eyes with clinically significant macular edema had received photocoagulation treatment in more recent periods of observation compared to earlier periods (Klein R, unpublished data).

Glycemic control at baseline and throughout the study period was strongly related to incidence of VI. This is consistent with our earlier findings and with findings from other studies.^{5,7,11,32} While controlling for other factors, each percentage-point increase in the HbA1 level at baseline in our study was associated with a 28% increase in the 25-year incidence of any VI, while each percentage-point increase in the glycosylated hemoglobin A1 level at baseline was associated with a 27% increase in doubling of the visual angle in our study. We found similar results in models that updated HbA1 and changes in it between examinations at each interval of evaluation.

At the time of the 14-year follow-up of the cohort, we reported a univariate association of pack-years smoked after being diagnosed with diabetes which was no longer statistically significant after controlling for other risk factors.¹¹ With the longer follow-up, while controlling for DR severity, glycemic control, and other risk factors, current smoking at baseline was found to increase the risk of incident VI by 63%. Smoking has never been found to be associated with the incidence and progression of DR in the WESDR.¹⁹ While smoking may not affect severity of retinopathy, its hypoxic effect may independently have an effect on vision.³³ It is also possible that smoking may have resulted in increased incidence of cataract, explaining, in part, this relationship. This relationship of smoking to cataract has been found in the general population.³⁴ However, the association remained, although attenuated, when controlling for cataract status.

The relation of hypertension to the higher incidence of VI was not unexpected. In the WESDR, presence of hypertension was associated with a 73% increase in the risk of incident proliferative DR.²¹ However, while a beneficial effect of lowering blood pressure on progression of DR and reduction in loss of vision has been shown in persons with type 2 DM, randomized controlled clinical trials have not shown a similar effect in persons with type 1 DM.^{35–39} Regardless of the effect of blood pressure on visual impairment, intensive control of blood pressure has been shown to be beneficial in reducing morbidity (myocardial infarction, stroke and nephropathy) and mortality.

There are many strengths of the study, including a large cohort with a broad distribution of severity of DR at baseline, a low refusal rate, and use of standardized protocols of measurement which included objective recording of VI using ETDRS protocols. However, caution should be observed when interpreting the findings from our study. Mortality may affect the relation of risk factors to incidence of endpoints. Because HbA1, blood pressure, gross proteinuria, and retinopathy severity level are significantly associated with incident VI and decreased survival,⁴⁰ it is likely that the effect of death would diminish the strength of these relationships.

In summary, our data suggest that better glycemic control, and to a lesser extent, not smoking and blood pressure control may be beneficial in reducing the incidence of VI in people with T1DM. Decreasing estimates of annualized incidence of VI in the cohort may reflect changes in management of DR. These data are important in planning for future needs for care and associated costs in persons with T1DM who develop VI.

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Figure 1.

The 25-year change in the mean number of letters read correctly read in right eyes by duration of diabetes at baseline in the Wisconsin Epidemiologic Study of Diabetic Retinopathy. Box extends from 25th to 75th percentiles with line at median. Mean change indicated by star.

Figure 2.

The 25-year change in the mean number of letters read correctly read in right eyes by severity of diabetic retinopathy at baseline in the Wisconsin Epidemiologic Study of Diabetic Retinopathy. Box extends from 25th to 75th percentiles with line at median. Mean change indicated by star.

Figure 3.

Estimated annual rates for incidence of any and severe visual impairment for 4 periods of the Wisconsin Epidemiologic Study of Diabetic Retinopathy. Width of bar corresponds to length of period.

Table 1

Twenty-five Year Cumulative Incidence of Any and Severe Visual Impairment and Doubling of the Visual Angle in Better Eye by Age and Duration of Diabetes in the Wisconsin Epidemiologic Study of Diabetic Retinopathy.

	Incidence of Any Visual Impairment					Incidence of Double of Visual Angle					Incidence of Severe Visual Impairment				
	Cumulative Incidence (%)					Cumulative Incidence (%)					Cumulative Incidence (%)				
	No. at Risk	No. Events	Event	Risk of Dying Before Event		No. at Risk	No. Events	Event	Risk of Dying Before Event		No. at Risk	No. Events	Event	Risk of Dying Before Event	
All Groups	874	105	13.3	27.3		939	126	15.1	30.3		920	21	2.5	36.6	
0-9 years	24	0	0.0	0.0		25	0	0.0	0.0		25	0	0.0	0.0	
10-14 years	77	3	5.5	13.7		80	4	7.6	13.3		80	1	2.3	15.6	
15-19 years	145	5	3.8	20.6		147	10	7.8	19.1		147	1	1.0	22.1	
20-24 years	145	16	13.0	11.0		153	26	19.9	11.8		153	5	3.4	16.1	
25-29 years	129	18	14.7	22.2		136	19	14.8	24.7		135	4	3.2	31.8	
30-34 years	131	16	14.7	28.7		140	14	11.8	33.9		137	0	0.0	36.0	
35+ years	223	47	21.9	48.8		258	53	21.6	54.0		243	10	4.2	67.0	
Diabetes Duration															
0-2 years	74	5	8.5	8.8		75	6	10.6	8.7		75	0	0.0	14.6	
3-4 years	82	5	9.1	14.1		83	6	10.1	13.9		83	1	1.6	14.1	
5-9 years	232	15	8.0	16.3		237	23	12.4	15.3		237	1	0.6	18.3	
10-14 years	159	14	9.3	18.5		164	21	13.8	19.7		164	3	1.9	24.2	
15-19 years	114	18	16.7	29.0		130	23	18.5	32.2		127	8	6.8	29.8	
20-24 years	73	11	16.2	44.2		81	13	17.4	47.3		78	5	6.9	53.7	
25-29 years	63	9	15.4	60.8		76	12	16.7	59.6		70	3	4.3	69.4	
30+ years	77	28	37.2	55.7		93	22	24.5	69.6		86	0	0.0	90.9	

Table 2

Associations with the 25-year Cumulative Incidence of Any Visual Impairment in the Wisconsin Epidemiologic Study of Diabetic Retinopathy.*

Risk variable	Level	Controlling for only Duration of Diabetes			Multivariate*		
		HR	95% CI	P	HR	95% CI	P
Sex	Male	1.10	0.75–1.61	0.62			
Glycosylated hemoglobin A _{1c}	Per 1%	1.33	1.21–1.46	<0.001	1.28	1.16–1.42	<0.001
Glycosylated hemoglobin A _{1c} quartiles	9.5–10.5 vs <9.5%	1.61	0.80–3.23	0.18			
	10.6–12.0 vs <9.5%	1.83	0.93–3.60	0.08			
	12.1–19.5 vs <9.5%	4.33	2.32–8.07	<0.001			
Proteinuria	Present	2.90	1.92–4.37	<0.001			
Retinopathy severity	21 vs 10	1.62	0.77–3.44	0.21			
	31–37 vs 10	1.86	0.92–3.78	0.08			
	43–53 vs 10	3.19	1.50–6.77	0.003			
	60+ vs 10	8.26	4.22–16.17	<0.001			
	Per 2 steps	1.35	1.25–1.46	<0.001	1.14	1.03–1.27	0.01
Cataract	Present	3.68	2.37–5.70	<0.001	2.49	1.53–4.04	<0.001
History of Glaucoma	Present	3.92	0.96–16.03	0.06			
Systolic Blood Pressure	Per 10 mmHg	1.40	1.27–1.55	<0.001			
Diastolic Blood Pressure	Per 10 mmHg	1.53	1.27–1.83	<0.001			
Hypertension	Present	2.74	1.82–4.12	<0.001	1.72	1.05–2.83	0.03
Smoking History [†]	Past vs never	1.24	0.72–2.11	0.44			
Pack Years Smoked [‡]	Current vs never	1.69	1.09–2.61	0.02	1.63	1.01–2.61	0.04
	<5 pack-years	0.90	0.49–1.65	0.73			
	5–14 pack-years vs never	1.26	0.68–2.31	0.46			
Pack Year Smoked	≥15 pack-years vs never	2.26	1.36–3.74	0.002			
	Per 1 SD	1.38	1.17–1.64	<0.001			
	Per 1 SD	1.08	0.89–1.30	0.435			

* All variables included in a single model. Missing rows indicate that variable was not significant and thus not included in the final multivariate model.

[†] Restricted to those 18 years and older.

Abbreviations: HR=hazard ratio; CI=confidence interval; SD=standard deviation.

Table 3

Associations with the 25-year Cumulative Incidence of Controlling Only for Duration of Diabetes in the Wisconsin Epidemiologic Study of Diabetic Retinopathy.*

Risk variable	Level	Doubling of Visual Angle			Multivariate*		
		HR	95% CI	P	HR	95% CI	P
Sex	Male	1.01	0.72–1.40	0.98			
Glycosylated hemoglobin A ₁	Per 1%	1.29	1.20–1.40	<0.001	1.27	1.10–2.70	0.02
Glycosylated hemoglobin A ₁ quartiles	9.5–10.5 vs < 9.5%	2.16	1.22–3.84	0.01			
	10.6–12.0 vs < 9.5%	1.93	1.09–3.43	0.02			
	12.1–19.5 vs < 9.5%	3.56	2.07–6.11	<0.001			
Proteinuria	Present	3.24	2.26–4.65	<0.001	1.84	1.14–2.96	0.01
Retinopathy severity	21 vs 10	1.65	0.89–3.07	0.11			
	31–37 vs 10	1.80	1.00–3.26	0.05			
	43–53 vs 10	3.15	1.67–5.93	<0.001			
	60+ vs 10	6.81	3.88–11.95	<0.001			
	Per two steps	1.31	1.23–1.40	<0.001	1.10	1.00–1.21	0.05
Cataract	Present	3.03	2.06–4.48	<0.001	1.72	1.10–2.70	0.02
History of Glaucoma	Present	7.77	3.60–16.80	<0.001	5.56	1.23–25.16	0.03
Systolic Blood Pressure	Per 10 mmHg	1.30	1.20–1.42	<0.001			
Diastolic Blood Pressure	Per 10 mmHg	1.41	1.21–1.65	<0.001			
Hypertension	Present	2.61	1.82–3.75	<0.001			
Smoking History [†]	Past vs never	1.17	0.72–1.91	0.53			
	Current vs never	1.60	1.09–2.34	0.02	1.48	0.97–2.27	0.07
	<5 pack-years	0.98	0.59–1.64	0.95			
Pack Years Smoked [†]	5–14 pack-years vs never	1.34	0.79–2.28	0.28			
	≥15 pack-years vs never	2.05	1.28–3.27	0.003			
Pack Year Smoked	Per 1 SD	1.37	1.17–1.69	<0.001			
Body mass index	Per 1 SD	1.13	0.96–1.32	0.14			

* All variables included in a single model. Missing rows indicate that variable was not significant and thus not included in the final multivariate model.

[†] Restricted to those 18 years and older.

Abbreviations: HR=hazard ratio; CI=confidence interval; SD=standard deviation