Risk Factors for High-Risk Proliferative Diabetic Retinopathy and Severe Visual Loss: Early Treatment Diabetic Retinopathy Study Report #18

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Purpose. To identify risk factors for the development of high-risk proliferative diabetic retinopathy (PDR) and for the development of severe visual loss or vitrectomy (SVLV) in eyes assigned to deferral of photocoagulation in the Early Treatment Diabetic Retinopathy Study (ETDRS).

Methods. Multivariable Cox models were constructed to evaluate the strength and statistical significance of baseline risk factors for development of high-risk PDR and of SVLV.

Results. The baseline characteristics identified as risk factors for high-risk PDR were increased severity of retinopathy, decreased visual acuity (or increased extent of macular edema), higher glycosylated hemoglobin, history of diabetic neuropathy, lower hematocrit, elevated triglycerides, lower serum albumin, and, in persons with mild to moderate nonproliferative retinopathy, younger age (or type 1 diabetes). The predominant risk factor for development of SVLV was the prior development of high-risk PDR. The only other clearly significant factor was decreased visual acuity at baseline. In the eyes that developed SVLV before high-risk proliferative retinopathy was observed, baseline risk factors were decreased visual acuity (or increased extent of macular edema), older age (or type 2 diabetes), and female gender.

Conclusions. These analyses supported the view that the retinopathy-inhibiting effect of better glycemic control extends across all ages, both diabetes types, and all stages of retinopathy up to and including the severe nonproliferative and early proliferative stages and the possibility that reducing elevated blood lipids and treating anemia slow the progression of retinopathy. (*Invest Ophthalmol Vis Sci.* 1998;39:233-252)

The Early Treatment Diabetic Retinopathy Study (ETDRS), a randomized clinical trial of photocoagulation and aspirin in patients with mild to severe nonproliferative diabetic retinopathy (NPDR) or early proliferative diabetic retinopathy (PDR), enrolled 3711 patients and followed them for 3 to 9 years.[1-4] Patients were assigned randomly to aspirin or placebo. One eye of each patient was assigned randomly to early photocoagulation and the other to deferral of photocoagulation unless high-risk PDR, as defined in the Diabetic Retinopathy Study (DRS),[5] developed (see Table 1). In a previous report,[6] retinopathy features, documented in color stereoscopic fundus photographs taken at the baseline examination in eyes assigned to deferral, were evaluated as risk factors for the progression of retinopathy in these eyes, and a retinopathy severity scale was developed. The purpose of this report is to identify additional factors associated with the risk for progression of retinopathy to the high-risk PDR stage and with the risk for development of severe visual loss in these eyes. As in a previous report,[3] patients assigned to aspirin were pooled with those assigned to placebo, because aspirin was not found to have any effect on retinopathy progression.

Advantages of the ETDRS cohort for risk factor analyses are its large size, the inclusion of patients with retinopathy at clinically important stages, frequent follow-up over a period of several years, small losses to follow-up, and good documentation of retinopathy severity. Limitations are that the study was not population based, that patients who had retinopathy less severe in either eye than mild NPDR or who had a poor prognosis for 5-year survival were excluded, and that some eyes assigned to deferral of photocoagulation had focal photocoagulation for clinically significant macular edema after the protocol was changed in 1985 to allow such treatment.

Methods

Study Design

From April 1980 to July 1985, the ETDRS enrolled 3711 patients who had a clinical diagnosis of diabetes mellitus, were 18

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to 69 years of age, had a favorable prognosis for 5-year survival, and had retinopathy in each eye that was defined as having either no macular edema, visual acuity of 20/40 or better, and moderate to severe NPDR or mild to moderate PDR (see Table 1); or macular edema (defined in this context as retinal thickening or hard exudates located within 1 disc diameter of the center of the macula), visual acuity of 20/200 or better, and mild, moderate, or severe NPDR or mild to moderate PDR.[2] Patients were eligible if both eyes met one of these definitions or if one eye met one definition and the fellow eye the other. The study followed the principles of the Declaration of Helsinki and was approved by the institutional review boards for research in human subjects of the participating centers. Before enrollment, all patients gave written consent after receiving written and verbal information concerning their disease and the study.

Baseline examinations included best corrected visual acuity, ophthalmoscopy, seven-field nonsimultaneous stereoscopic color fundus photography, fluorescein angiography, a general medical examination, and laboratory tests including hemoglobin A_{1c} (HbA_{1c}). Baseline laboratory tests were discontinued in September 1983, after the first 2709 patients had been enrolled. All patients were assigned randomly to a group administered either 650 mg aspirin per day or placebo. One eye of each patient was assigned randomly to early photocoagulation and the other eye to deferral of photocoagulation—that is, careful follow-up and prompt scatter photocoagulation if high-risk PDR developed. Follow-up visits were scheduled 6 weeks and 4 months after enrollment and every 4 months thereafter. At each visit, the best-corrected visual acuity was measured and ophthalmoscopy was carried out to detect the development of high-risk PDR. Photographs were taken at the 4- and 12-month visits and annually thereafter and were graded centrally.[7] Clinics were notified when the gradings detected high-risk PDR. In August 1985, the protocol was modified to encourage prompt focal photocoagulation for clinically significant macular edema in eyes assigned to deferral of photocoagulation. Details of the study design, methods, and results of the trial have been described previously.[1-4,6-13]

Outcome Measures

The outcome measures used in these analyses were development of high-risk PDR and of severe visual loss or vitrectomy (SVLV) in eyes assigned to deferral of photocoagulation. Severe visual loss was defined as best-corrected visual acuity less than 5/200 at two consecutively completed 4-month follow-up visits and was counted as an event at the first of these visits. Severe visual loss and vitrectomy were combined because vitrectomy saved from severe visual loss an unknown number of eyes in which it otherwise would have developed and because vitrectomy is an unfavorable outcome in eyes eligible for the ETDRS. Preliminary analyses confirmed the expectation that most eyes developing SVLV first developed high-risk PDR, which was a much more frequent event (during the first 5 years of follow-up, high-risk PDR developed in the eye assigned to deferral of photocoagulation in 36.8% of the 3711 patients, whereas SVLV developed in 5.3%). Therefore, we analyzed risk factors for high-risk PDR first and then factors for SVLV.

Retinopathy Severity Scale

In evaluating progression to a specified stage in any gradually progressive disease, persons entering a study just below that stage would be expected to be at higher risk for such progression than those entering at earlier stages. Accordingly, severity of retinopathy at baseline is likely to be a strong risk factor for development of high-risk PDR and thus an important factor to include when evaluating other possible risk factors. It has been recognized that the retinopathy severity scale developed in the ETDRS (Table 1) has two important shortcomings as a predictor of the development of high-risk PDR: Eyes with very severe NPDR (level 53E) were at greater risk than those with mild PDR (level 61), which was a higher step on the scale[4]; and the intraretinal characteristics predictive of progression from NPDR to PDR (hemorrhages and/or microaneurysms, venous beading, and intraretinal microvascular abnormalities) were ignored in eyes with PDR, even though these characteristics were clearly related to the risk of progression from non-high-risk to high-risk PDR.[6]

These relationships can be seen in Table 2, which presents proportions of eyes assigned to deferral of photocoagulation developing high-risk PDR at or before the 3-year visit. This information was used to develop a modified retinopathy severity scale (Table 3), in which the first three steps are identical with levels 35, 43, and 47 previously defined using ETDRS data (Table 1).[6] In Table 2 these three steps are pooled, and the 3-year rate of high-risk PDR for these 2437 patients was 15.3% (for levels 35, 43, and 47, respectively, the rates were 6.4%, 13.3%, and 23.3%). Rates were higher and very similar for the 498 eyes with NPDR in level 53A-D (37.8%) and for the 167 eyes with PDR in level 61 and free of the intraretinal characteristics of severe NPDR (37.7%). The 1- and 5-year rates were also similar in these categories, and they were combined and designated step 4 in the revised retinopathy severity scale (see Table 3). The 3-year rates were similar for the 119 eyes with PDR in level 61 and intraretinal characteristics that would, if PDR were not present, place them in level 53A-D (54.6%) and for the 129 eyes with PDR in level 65 and free of the intraretinal characteristics of severe NPDR (55.0%). The 1- and 5-year rates were similar in these categories, and they were combined as step 5 in the revised scale. The 3-year rates shown in Table 2 for the remaining four categories are also similar to each other, as were the 1- and 5-year rates, and they were combined as step 6 of the revised scale.

Diabetes Type

In a previous report, the ETDRS developed definitions of diabetes types based on age at diagnosis, insulin use, and weight, using Sustacal (Mead Johnson Nutritionals, Evansville, IN)-stimulated C-peptide measurements in a subset of 582 patients as the standard against which alternative definitions were compared.[11] Two types of definitions were proposed—"broad" definitions, which assigned all patients to either type 1 (insulin-dependent) or type 2 (non-insulin-dependent) diabetes, and more restrictive definitions, which divided patients into three groups ("strict" type 1, a "mixed" category for patients whose diabetes type was less certain, and "strict" type 2). We chose the three-group classification for this report, because it would be expected to maximize the difference between type 1 and type 2 diabetes. Patients whose diabetes was diagnosed when they were 30 years of age or younger, who began insulin within 1 year of diagnosis and used it continuously thereafter, and who were not overweight (120% of desirable body weight) were classified as type 1. Patients who were 31 years of age or older at diagnosis and who did not take insulin, or took it only intermittently, and those who were 41 years of age or older at

TABLE 1. Abbreviated Summary of the Early Treatment Diabetic Retinopathy Study Scale of Diabetic Retinopathy Severity for Individual Eyes

Level	*Severity*	*Definition*
10	No retinopathy	Diabetic retinopathy absent
20	Very mild NPDR	Microaneurysms only
35*	Mild NPDR	Hard exudates, cotton-wool spots, and/or mild retinal hemorrhages
43	Moderate NPDR	43A Retinal hemorrhages moderate (>photograph 1†) in four quadrants or severe (≥photograph 2A) in one quadrant 43B Mild IRMA (<photograph 8A) in one to three quadrants
47	Moderate NPDR	47A Both level 43 characteristics 47B Mild IRMA in four quadrants 47C Severe retinal hemorrhages in two to three quadrants 47D Venous beading in one quadrant
53A-D	Severe NPDR	53A ≥2 level 47 characteristics 53B Severe retinal hemorrhages in four quadrants 53C Moderate to severe IRMA (≥photograph 8A) in at least one quadrant 53D Venous beading in at least two quadrants
53E	Very severe NPDR	≥2 level 53A-D characteristics
61	Mild PDR	NVE < 0.5 disc area in one or more quadrants
65	Moderate PDR	65A NVE ≥ 0.5 disc area in one or more quadrants 65B NVD <photograph 10A (<0.25-0.33 disc area)
71, 75	High-risk PDR	NVD ≥photograph 10A, or NVD <photograph 10A or NVE ≥ 0.5 disc area plus VH or PRH, or VH or PRH obscuring ≥ 1 disc area
81, 85	Advanced PDR	Fundus partially obscured by VH and either new vessels ungradable or retina detached at the center of the macula

NPDR, nonproliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; IRMA, intraretinal microvascular abnormalities; NVE, new vessels elsewhere; NVD, new vessels on or within 1-disc diameter of the optic disc; PRH, preretinal hemorrhage; VH, vitreous hemorrhage. The definition for each level assumes that the definition for any higher level is not met.

*NPDR levels 35 and above, all require presence of microaneurysms.[6]

†See reference 7 for standard photographs.

diagnosis and were overweight (whether or not they took insulin) were classified as type 2. All others were classified as mixed type.

Race–Ethnicity

In these analyses, persons identifying themselves as "black" and "Hispanic" were combined in a "nonwhite" category because of small numbers (330 in the former and 220 in the latter) and because 5-year rates of high-risk PDR were similar in the two groups in each baseline retinopathy severity step. The 27 patients who placed themselves in other race-ethnicity categories were also included in the nonwhite category.

Medical and Laboratory Evaluations

The baseline medical history and examinations were carried out by or under the supervision of a study internist, and specified findings were recorded on a form. The review of systems included a history of diabetic neuropathy, defined as a

TABLE 2. Percentage of Eyes Assigned to Deferral of Photocoagulation Developing High-Risk Proliferative Diabetic Retinopathy at or before the 3-Year Visit

	Severity of NPDR Characteristics					
	Levels 35–47		*Level 53A–D*		*Level 53E*	
*Severity of PDR**	*No. at Baseline*	*High-Risk PDR by 3-year Visit (%)*	*No. at Baseline*	*High-Risk PDR by 3-year Visit (%)*	*No. at Baseline*	*High-Risk PDR by 3-year Visit (%)*
No PDR	2437	15.3	498	37.8	92	62.0
Level 61	167	37.7	119	54.6	52	61.5
Level 65	129	55.0	103	66.0	83	74.7

NPDR, nonproliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy.

*See Table 1 for definitions.

TABLE 3. Revised Retinopathy Severity Scale Used in This Report

Step Severity	*Severity Level on ETDRS Final Scale*
1	35*
2	43
3	47
4	53A-D, or 61 with intraretinal characteristics < level 53
5	61 with intraretinal characteristics of level 53A-D, or 65 with intraretinal characteristics < level 53
6	53E, or 61 with intraretinal characteristics of level 53E, or 65 with intraretinal characteristics of level 53A-D, or 65 with intraretinal characteristics of level 53E

*One patient, with baseline severity graded at level 20, was included in this step.

history of any of the following: persistent paresthesias of the limbs, nocturnal limb pain or cramps, symptomatic postural hypotension, impotence or bladder dysfunction diagnosed as related to diabetes. Patients who had undergone or who were candidates for renal transplantation or dialysis were excluded from the trial. Blood counts and urinalyses were performed at each clinical center, and all other laboratory tests (glucose, serum lipids [cholesterol, cholesterol components, triglyceride], plasma proteins [albumin, fibrinogen, α_2-macroglobulin], creatinine, HbA_{1c}, uric acid) were carried out at a central laboratory.

Statistical Methods

Of the 3711 patients enrolled, 22 were excluded because of some missing baseline information and 9 were excluded because detailed gradings of baseline fundus photographs after enrollment indicated the presence of high-risk PDR at baseline. Of the remaining 3680 patients, 2654 had baseline HbA_{1c} measurements; because of the potential importance of HbA_{1c}, most analyses are presented for this group. Missing laboratory data in these 2654 patients were handled by applying mean imputation to each indicator variable included in the Cox models.[14]

The principal outcome variables for analysis were the time to development of high-risk PDR and the time to development of SVLV, that is, the interval in months between baseline and the scheduled follow-up visit at which the specified event was first observed. Occasionally, the event was observed at an unscheduled visit; in such cases the event was counted as occurring at the nearest scheduled visit. Patients without the outcome were censored at the last study visit or at death. Incidence rates (both cumulative and annual) were calculated using a competing risks model to account for mortality (which precludes the development of high-risk PDR). The cumulative incidence rate is an estimate of the proportion of patients (available at baseline) in whom high-risk PDR developed by the end of each follow-up period. The annual incidence rate is an estimate of the proportion of patients available at the start of each follow-up period (alive and free of high-risk PDR) in whom high-risk PDR developed by the end of the follow-up period. In steps with high early rates of developing high-risk PDR, the estimates of the annual incidence rates in later years are based on smaller samples than those in earlier years and are thus less precise. The precision of the estimate is reflected by the width of the confidence interval. Confidence intervals and hypothesis tests for incidence rates were based on the natural logarithms of the rates, under the assumption that these followed an approximately normal distribution.

Multivariable Cox models for discrete failure time were constructed to evaluate the strength and statistical significance of risk factors for the development of high-risk PDR (SAS PROC PHREG with ties = discrete).[15,16] Models for high-risk PDR used one of two alternative follow-up periods: the first 2 years of follow-up only, when the effect of retinopathy severity was greater, and the first 5 years of follow-up, during which 87.1% of high-risk PDR events and 77.7% of SVLV events occurred. By using two follow-up periods, we could evaluate the validity of the underlying model, which assumes constant effects over the entire follow-up time. Detailed information will be presented only for the 5-year follow-up period. Models for SVLV used all follow-up time. For all analyses, all continuous variables were collapsed into discrete categories. By categorizing the continuous variables, we did not have to assume a particular functional form for the relationship between each variable and the development of high-risk PDR, and we minimized the impact of extreme values. The goal of the categorization was to create clinically relevant groups with substantial numbers of patients.

The initial models included 10 baseline variables selected because of their fundamental interest. These variables were retinopathy severity, age, gender, race, duration and type of diabetes, percentage of desirable weight, HbA_{1c}, extent of macular edema, and visual acuity. The main effects of these variables were retained in the initial models regardless of their statistical significance. Two-way interactions between retinopathy severity and each of the other variables, as well as the two-way interaction of duration and type of diabetes, were examined. These interactions were only included in the initial models if they were statistically significant at the 5% level for at least one of the two follow-up periods.

Thirty-seven additional baseline variables were considered for inclusion in the final models along with the 10 original variables. The effects of these variables were examined using single variable additions to the initial models and simultaneous modeling. For simultaneous modeling, a modified backwards selection procedure was used to decide which of these additional variables to include in the final models. The selection procedure consisted of the following steps: First, a saturated model was fit to each follow-up period; second, all variables that were not "significant at the 20% level" (calculated using the Efron approximation to the likelihood) in either follow-up period were removed from the current model, and this process was repeated until no more variables were removed; and third, all variables that were not significant at the 10% level in either follow-up period were removed from the current model, and this process was repeated until no more variables were removed. The selected models (one for each follow-up period) were then refit using the exact likelihood instead of the Efron approximation to become the final models, which included 21

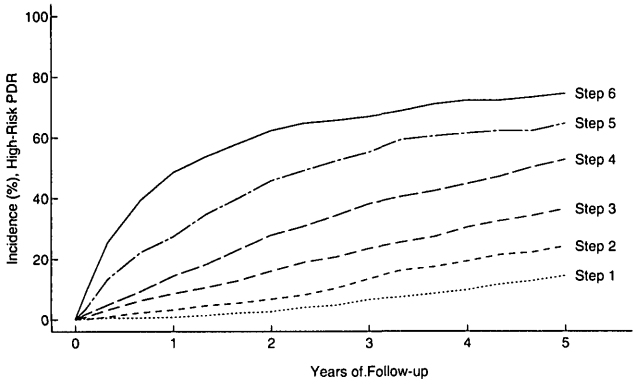

Figure 1. Cumulative life table rates of progression to high-risk PDR for each step in the revised retinopathy severity scale.

variables (the initial 10 and 11 more). Significance levels are also presented for single additions of each of these 11 variables to the initial models (calculated using the Efron approximation). The effects of the 26 variables excluded from the final models were further examined in "additional" models using single variable additions to the initial models.

Cumulative 5-year incidence rates of SVLV were calculated for each category of the 10 baseline variables selected a priori. Rates were calculated separately for SVLV at or after the occurrence of high-risk PDR and for SVLV occurring in the absence of high-risk PDR or before its occurrence. Models were constructed to evaluate the strength and statistical significance of these factors, and of the prior occurrence of high-risk PDR, for the development of SVLV.

These analyses were not the primary focus of the ETDRS, and many statistical tests were performed. Probability values are presented without adjusting for multiple testing. Thus, we will consider $P \leq 0.01$ to be nominally significant and will refer to P values in the 0.1 to 0.01 range as borderline. For incidence rates and odds ratios, 95% confidence intervals (95% CI) are provided for each level of the various baseline variables presented.

Results

Retinopathy Severity at Study Entry

Figure 1 shows cumulative life table rates of progression to high-risk PDR for each step in the revised retinopathy severity scale. Cumulative rates and annual incidence rates are shown in Table 4. For steps 1 and 2, the annual rates were low during the first 1 to 2 years and then increased. For steps 3 and 4, the 1-year rates were higher than for steps 1 and 2, and the annual rates appeared to remain approximately the same throughout 5 years. For step 5, and particularly for step 6, the annual rates were higher during the first 1 to 2 years and became lower thereafter. The difference in cumulative rates between steps 1 and 6 was approximately 60-fold at 1 year (0.8% and 48.5%, respectively) and approximately 5-fold at 5 years (14.3% and 74.4%, respectively).

Age at Study Entry and Diabetes Type

Because age and diabetes type are highly correlated (the correlation coefficient in our data set was 0.75), it may be difficult to determine which (if either) is a more important risk factor for progression. Figure 2 demonstrates the correlation between diabetes type and age and the difference in the distribution of these factors between retinopathy severity categories. Patients 39 years of age or younger were classified almost exclusively as type 1, whereas those 50 years of age or older were almost equally divided between mixed type and type 2, regardless of retinopathy severity category. The distributions of

Table 4. Cumulative Incidence and Annual Incidence of High-Risk Proliferative Diabetic Retinopathy by Retinopathy Severity Step. Estimated Percentage (95% Confidence Interval)*†

Step	*Total‡*	*1 Year*	*2 Year*	*3 Year*	*4 Year*	*5 Year*
1	607	0.8 (0.3-2.0)	2.7 (1.6-4.3)	6.5 (4.8-8.8)	9.7 (7.5-12.4)	14.3 (11.7-17.6)
			1.9 (1.3-3.4)	*4.1 (2.8-6.1)*	*3.6 (2.6-5.6)*	*5.7 (3.8-8.6)*
2	898	3.2 (2.3-4.6)	6.7 (5.3-8.6)	13.4 (11.3-15.8)	19.2 (16.8-22.0)	24.1 (21.4-27.2)
			3.7 (2.6-5.2)	*7.5 (5.9-9.6)*	*7.3 (5.6-9.6)*	6.9 (5.0-9.5)
3	932	8.5 (6.9-10.5)	15.9 (13.8-18.5)	23.4 (20.9-26.3)	30.4 (27.6-33.6)	36.5 (33.4-39.8)
			8.3 (6.6-10.4)	*9.4 (7.5-11.7)*	*10.0 (7.9-12.6)*	*9.9 (7.5-13.0)*
4	665	14.4 (11.9-17.3)	27.9 (24.7-31.5)	38.1 (34.6-42.0)	44.6 (41.0-48.6)	52.6 (48.9-56.7)
			16.1 (13.3-19.5)	*15.0 (12.0-18.7)*	*11.5 (8.7-15.3)*	*16.6 (12.7-21.7)*
5	248	27.4 (22.4-33.6)	45.7 (39.9-52.4)	55.2 (49.3-61.8)	61.4 (55.6-67.8)	64.7 (58.9-71.0)
			26.1 (20.3-33.5)	*19.0 (13.2-27.5)*	*16.1 (10.1-25.6)*	*10.9 (5.4-21.9)*
6	330	48.5 (43.3-54.2)	62.4 (57.3-67.8)	67.0 (62.1-72.3)	72.3 (67.5-77.3)	74.4 (69.8-79.4)
			27.6 (21.5-35.4)	*13.0 (8.1-20.9)*	*17.4 (11.3-26.8)*	*9.0 (4.2-19.3)*
All	3680	11.9 (10.9-12.9)	19.8 (18.6-21.1)	26.9 (25.5-28.4)	32.7 (31.2-34.2)	38.1 (36.5-39.7)
			9.2 (8.3-10.3)	*9.2 (8.2-10.4)*	*8.6 (7.6-9.8)*	*9.2 (7.9-10.6)*

*Estimates of crude cumulative incidence at specified follow-up visits and 95% confidence intervals on log(cumulative incidence) transformed back to cumulative incidence scale are given in non-italic type.

†Estimates of annual incidence (percentage of eyes without high-risk proliferative diabetic retinopathy [PDR] at the start of the interval developing high-risk PDR by the end of the interval) of high-risk PDR and 95% confidence interval on log(incidence) transformed back to the incidence scale are given in italic type.

‡Number of participants in each retinopathy severity step at baseline.

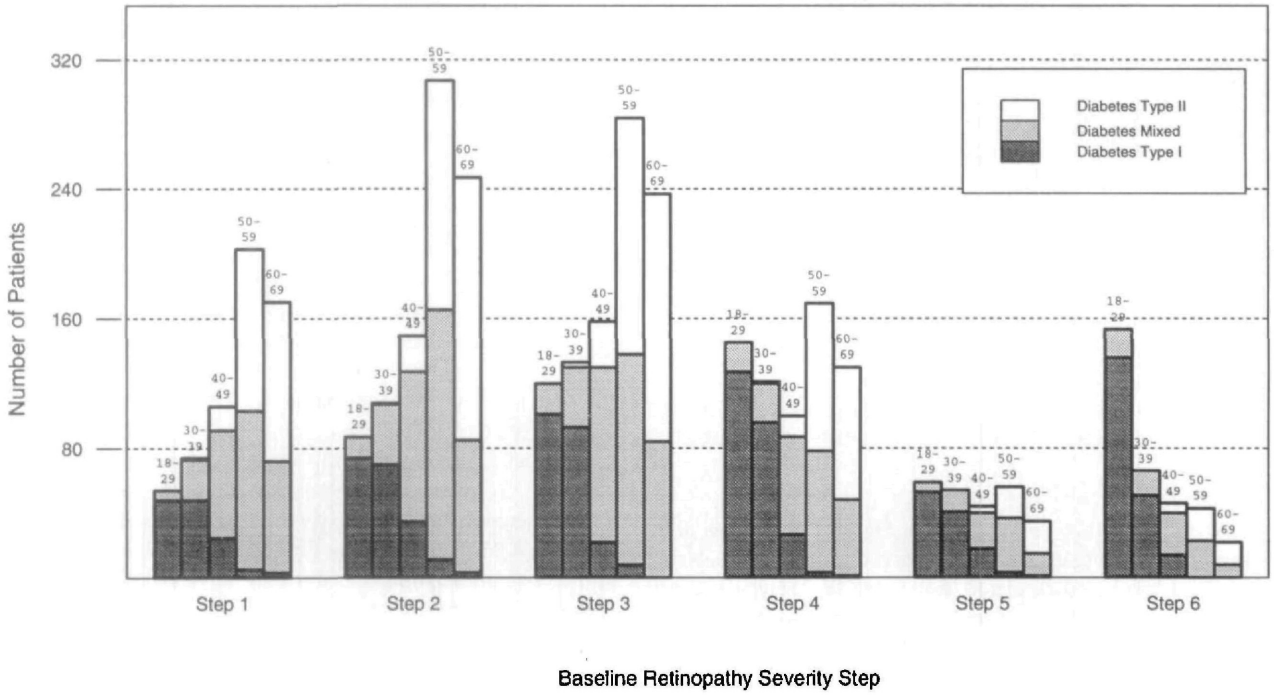

Figure 2. Baseline distribution of patients by age and diabetes type within each retinopathy severity step. Age band (in years) is indicated above each bar.

age and diabetes type were similar in retinopathy severity steps 1, 2, and 3, with older patients and type 2 diabetes predominating, but thereafter, as severity increased, younger age and type 1 diabetes became increasingly predominant. The relationships of age and diabetes type to the risk for high-risk PDR were examined within each retinopathy severity category (data not shown). Within steps 1 to 3 this risk decreased with increasing age and was lower in type 2 and mixed diabetes than in type 1 diabetes. These relationships weakened in step 4 and were not present in steps 5 and 6. Because the effects of age and diabetes type differed by retinopathy severity, further analyses were restricted to multivariable modeling, which used follow-up periods of 2 and 5 years (detailed results are presented below only for 5 years).

Other Baseline Factors

Seven additional variables were selected for their fundamental interest (gender, race-ethnicity, duration of diabetes, percentage of desirable weight, HbA_{1c}, extent of macular edema, and visual acuity) and were examined in multivariable Cox models that included retinopathy severity, age, and diabetes type (initial models, see Tables 5 and 7). In Table 5, odds ratios for the development of high-risk PDR within the first 5 years of follow-up are shown for age, gender and race-ethnicity within steps of the retinopathy severity scale, because the effects of these variables differed across the scale. The first entry in each cell of the table (italicized) gives the odds ratio in each step of the scale relative to step 1 within the specified age, gender, or race-ethnicity category. The odds of developing high-risk PDR in the first 5 years of follow-up for patients in step 6 compared with patients in step 1 ranged from 6.02 within the 18- to 29-year category to 52.4 within the 60- to 69-year category, and they were approximately 13 to 15 in all gender and race-ethnicity categories. The second entry in each cell gives the odds ratio in that category of the covariate relative to a risk of 1.00 in the first category within the specified step of the retinopathy severity scale. The odds in the 60- to 69-year age category relative to the 18- to 29-year category were 0.19 in retinopathy severity step 1. Risk decreased with increasing age within steps 1 to 4 of the scale. This effect was strong in steps 1 to 3, in which a 2.5- to 5-fold decrease in risk was found between the 18- to 29-year and the 60- to 69-year age groups. There was no evidence that the effect differed between these three severity levels ($P = 0.61$). The effect appeared smaller in step 4, tended to reverse in step 5, and was inconsistent in step 6; there was evidence that the effect differed between these three severity levels ($P = 0.0040$). The odds tended to be higher in women than in men in most retinopathy severity steps; the largest difference was in step 2, in which the odds ratio was 1.75 with a 95% CI of 1.26 to 2.41. There was little difference in risk between white and nonwhite race-ethnicity categories except in step 5, in which risk was decreased approximately 5-fold in the small group of nonwhite persons compared with those classified as white.

Additional discrete Cox models (final models) were constructed in which 37 additional baseline variables (listed in Figs. 6 and 7) were considered for addition to the 10 chosen for the initial models (see Methods). Eleven of the 37 additional variables had P values less than 0.1 in the 2- and/or 5-year models and were retained in the 5-year model presented in Tables 6 through 8 and Figures 3 through 6. The format of Table 6 is identical with that of Table 5, and the addition of the 11 variables led to virtually no change from the initial model in the effects of age, gender, or race-ethnicity. The age effects in the final model are shown graphically in Figure 3, and the gender and race-ethnicity effects are shown in Figure 4.

In Table 7 odds ratios are shown for the initial and final 5-year models for the six factors chosen a priori whose effects did not differ across steps of the retinopathy severity scale. For these factors as well, results of the two models were almost

Table 5. Initial Model for Developing High-Risk Proliferative Diabetic Retinopathy during 5 Years of Follow-Up (Factors with Effects That Vary by Retinopathy Severity)

	Step 1			*Step 2*			*Step 3*			*Step 4*			*Step 5*			*Step 6*		
	*N**	*OR†*	*(95% CI‡)*	*N**	*OR†*	*(95% CI‡)*	*N**	*OR†*	*(95% CI‡)*	*N**	*OR†*	*(95% CI‡)*	*N**	*OR†*	*(95% CI‡)*	*N**	*OR†*	*(95% CI‡)*
Age§,‖																		
18-29	41	*1.00*	(——)	60	*1.87*	*(0.87-4.03)*	89	*2.49*	*(1.21-5.12)*	98	*3.00*	*(1.47-6.11)*	50	*3.00*	*(1.41-6.37)*	112	*6.02*	*(3.00-12.1)*
		1.00	(——)		1.00	(——)		1.00	(——)		1.00	(——)		1.00	(——)		1.00	(——)
30-39	46	*1.00*	(——)	76	*2.13*	*(0.99-4.57)*	91	*2.25*	*(1.06-4.77)*	88	*3.85*	*(1.85-8.00)*	38	*4.31*	*(1.94-9.54)*	52	*10.9*	*(5.11-23.1)*
		0.84	(0.34-2.11)		0.96	(0.55-1.66)		0.76	(0.48-1.19)		1.08	(0.72-1.62)		1.21	(0.70-2.09)		1.52	(1.00-2.30)
40-49	63	*1.00*	(——)	115	*1.79*	*(0.91-3.52)*	112	*2.13*	*(1.10-4.13)*	79	*4.22*	*(2.18-8.18)*	35	*6.75*	*(3.22-14.1)*	36	*9.01*	*(4.41-18.4)*
		0.69	(0.29-1.63)		0.66	(0.38-1.13)		0.59	(0.37-0.94)		0.97	(0.62-1.49)		1.54	(0.86-2.78)		1.03	(0.62-1.69)
50-59	135	*1.00*	(——)	215	*1.75*	*(0.97-3.15)*	199	*3.03*	*(1.73-5.33)*	134	*5.56*	*(3.16-9.78)*	41	*19.5*	*(10.3-36.9)*	29	*11.9*	*(5.78-24.8)*
		0.42	(0.18-0.98)		0.40	(0.23-0.69)		0.52	(0.33-0.81)		0.79	(0.51-1.22)		2.76	(1.56-4.87)		0.84	(0.44-1.60)
60-69	131	*1.00*	(——)	180	*3.29*	*(1.47-7.36)*	169	*5.46*	*(2.50-11.9)*	97	*11.3*	*(5.13-24.7)*	27	*23.0*	*(9.32-56.6)*	16	*52.4*	*(20.4-134)*
		0.19	(0.07-0.51)		0.33	(0.11-0.61)		0.42	(0.26-0.68)		0.72	(0.44-1.17)		1.46	(0.74-2.88)		1.66	(0.82-3.33)
P Value¶					0.61									**0.0040**				
									< 0.0001									
Gender§,‖																		
Male	192	*1.00*	(——)	357	*1.95*	*(1.17-3.25)*	391	*3.44*	*(2.11-5.60)*	288	*5.60*	*(3.44-9.13)*	106	*13.0*	*(7.65-22.0)*	137	*14.8*	*(8.73-25.2)*
		1.00	(——)		1.00	(——)		1.00	(——)		1.00	(——)		1.00	(——)		1.00	(——)
Female	224	*1.00*	(——)	289	*2.35*	*(1.57-3.53)*	269	*2.60*	*(1.74-3.90)*	208	*5.05*	*(3.40-7.51)*	85	*7.09*	*(4.46-11.2)*	108	*13.4*	*(8.56-20.9)*
		1.45	(0.82-2.54)		1.75	(1.26-2.41)		1.09	(0.83-1.44)		1.30	(1.00-1.69)		0.79	(0.54-1.15)		1.30	(0.94-1.80)
P Value¶					0.091									0.071				
									<0.047									
Race/ethnicity§,‖,#																		
White	294	*1.00*	(——)	494	*1.95*	*(1.25-3.04)*	533	*3.43*	*(2.26-5.19)*	390	*5.89*	*(3.87-8.95)*	161	*17.7*	*(11.1-28.1)*	205	*13.9*	*(9.03-21.5)*
		1.00	(——)		1.00	(——)		1.00	(——)		1.00	(——)		1.00	(——)		1.00	(——)
Nonwhite	122	*1.00*	(——)	152	*1.58*	*(0.79-3.15)*	127	*2.83*	*(1.44-5.53)*	106	*3.79*	*(1.98-7.24)*	30	*3.45*	*(1.45-8.21)*	40	*15.0*	*(7.57-29.9)*
		1.13	(0.61-2.11)		0.92	(0.62-1.36)		0.93	(0.64-1.36)		0.73	(0.52-1.03)		0.22	(0.11-0.44)		1.22	(0.74-2.02)
P Value¶					0.84									**0.0004**				
									<0.0023									

*Number of participants with each risk factor combination at baseline.

†Odds ratio (OR) for developing high-risk characteristics during 5 years of follow-up from the Cox discrete failure time model, which includes these main effects and interactions and the main effects of HbA_{Ic}, type and duration of diabetes, desirable weight (%), visual acuity, and extent of macular edema.

‡95% confidence interval (CI) for the given odds ratio.

§Odds ratios in italics are relative to retinopathy severity step 1 within this category of the covariate, averaging (weighted by observed frequencies) over all categories of the other two covariates.

‖Odds ratios in non-italic type are relative to the first category of the covariate within the given retinopathy severity step.

¶*P* values are given for three different hypothesis tests. The first line of *P* values represents tests for homogeneity of effect within retinopathy severity steps 1 to 3 and 4 to 6, respectively. The second line is the *P* value for a test of homogeneity of effect across all six severity steps.

#"White" is the answer to the question of "race/ethnicity" of "white, not of Hispanic origin" (total 2077); nonwhite is answer of "American Indian or Alaskan native" (total 10), "Asian or Pacific Islander" (total 17), "black, not of Hispanic origin" (total 330), or "Hispanic" (total 220).

Table 6. Final Model for Developing High-Risk Proliferative Diabetic Retinopathy during 5 Years of Follow-Up (Factors with Effects that Vary by Retinopathy Severity)

	Step 1		*Step 2*		*Step 3*		*Step 4*		*Step 5*		*Step 6*	
	*N**	*OR† (95% CI‡)*	*N**	*OR† (95% CI‡)*	*N**	*OR† (95% CI‡)*	*N**	*OR† (95% CI‡)*	*N**	*OR† (95% CI‡)*	*N**	*OR† (95% CI‡)*
Age§,‖												
18-29	41	*1.00 (——)* 1.00 (——)	60	*1.93 (0.89-4.20)* 1.00 (——)	89	*2.79 (1.34-5.80)* 1.00 (——)	98	*3.31 (1.61-6.83)* 1.00 (——)	50	*2.94 (1.36-6.34)* 1.00 (——)	112	*6.35 (3.12-12.9)* 1.00 (——)
30-39	46	*1.00 (——)* 0.85 (0.34-2.16)	76	*2.24 (1.04-4.82)* 0.99 (0.57-1.72)	91	*2.28 (1.07-4.86)* 0.70 (0.44-1.10)	88	*3.71 (1.78-7.76)* 0.98 (0.63-1.44)	38	*4.45 (1.99-9.93)* 1.29 (0.74-2.25)	52	*10.4 (4.87-22.4)* 1.40 (0.92-2.14)
40-49	63	*1.00 (——)* 0.65 (0.27-1.57)	115	*1.69 (0.86-3.33)* 0.57 (0.33-0.99)	112	*2.20 (1.13-4.28)* 0.51 (0.32-0.83)	79	*4.37 (2.25-8.51)* 0.86 (0.55-1.34)	35	*7.28 (3.44-15.4)* 1.61 (0.88-2.96)	36	*9.83 (4.79-20.2)* 1.01 (0.61-1.67)
50-59	135	*1.00 (——)* 0.44 (0.19-1.02)	215	*1.66 (0.92-3.01)* 0.38 (0.22-0.66)	199	*2.83 (1.61-4.99)* 0.44 (0.28-0.71)	134	*5.10 (2.89-9.00)* 0.67 (0.43-1.06)	41	*18.4 (9.62-35.1)* 2.74 (1.52-4.95)	29	*9.74 (4.65-20.4)* 0.67 (0.34-1.31)
60-69	131	*1.00 (——)* 0.19 (0.07-0.51)	180	*3.21 (1.44-7.16)* 0.31 (0.17-0.57)	169	*5.17 (2.38-11.2)* 0.35 (0.21-0.58)	97	*11.2 (5.13-24.5)* 0.64 (0.38-1.06)	27	*23.2 (9.42-57.4)* 1.49 (0.74-2.99)	16	*63.3 (24.5-163)* 1.87 (0.92-3.83)
P Value¶				0.70						**0.0009**		
						< 0.0001						
Gender§,‖												
Male	192	*1.00 (——)* 1.00 (——)	357	*1.82 (1.09-3.04)* 1.00 (——)	391	*3.27 (2.01-5.33)* 1.00 (——)	288	*5.27 (3.23-8.59)* 1.00 (——)	106	*12.3 (7.22-20.9)* 1.00 (——)	137	*14.3 (8.43-24.4)* 1.00 (——)
Female	224	*1.00 (——)* 1.26 (0.71-2.22)	289	*2.48 (1.64-3.71)* 1.70 (1.22-2.37)	269	*2.74 (1.82-4.11)* 1.05 (0.79-1.40)	208	*5.34 (3.57-7.99)* 1.27 (0.97-1.67)	85	*7.60 (4.74-12.2)* 0.78 (0.52-1.15)	108	*14.0 (8.94-22.0)* 1.23 (0.88-1.72)
P Value¶				0.083						**0.097**		
						0.059						
Race/ethnicity§,‖,#												
White	294	*1.00 (——)* 1.00 (——)	494	*1.90 (1.22-2.97)* 1.00 (——)	533	*3.36 (2.22-5.09)* 1.00 (——)	390	*5.59 (3.67-8.51)* 1.00 (——)	161	*17.7 (11.1-28.2)* 1.00 (——)	205	*13.9 (9.00-21.4)* 1.00 (——)
Nonwhite	122	*1.00 (——)* 1.10 (0.59-2.07)	152	*1.49 (0.74-2.98)* 0.86 (0.58-1.29)	127	*2.84 (1.44-5.56)* 0.93 (0.64-1.36)	106	*4.09 (2.12-7.86)* 0.81 (0.57-1.15)	30	*3.17 (1.31-7.68)* 0.20 (0.10-0.40)	40	*15.4 (7.69-31.0)* 1.23 (0.74-2.05)
P Value¶				0.81						**0.0002**		
						0.0018						

*Number of participants with each risk factor combination at baseline.

†Odds ratio (OR) for developing high-risk characteristics during 5 years of follow-up from the Cox discrete failure time model, which includes these main effects and interactions and the main effects of HbA_{Ic}, type and duration of diabetes, desirable weight (%), visual acuity, and extent of macular edema.

‡95% confidence interval (CI) for the given odds ratio.

§Odds ratios in italics are relative to retinopathy severity step 1 within this category of the covariate, averaging (weighted by observed frequencies) over all categories of the other two covariates.

‖Odds ratios in non-italic type are relative to the first category of the covariate within the given retinopathy severity step.

¶*P* values are given for three different hypothesis tests. The first line of *P* values represents tests for homogeneity of effect within retinopathy severity steps 1 to 3 and 4 to 6, respectively. The second line is the *P* value for a test of homogeneity of effect across all six severity steps.

#"White" is the answer to the question of "race/ethnicity" of "white, nor not of Hispanic origin" (total 2077); nonwhite is answer of "American Indian or Alaskan native" (total 10), "Asian or Pacific Islander" (total 17), "black, not of Hispanic origin" (total 330), or "Hispanic" (total 220).

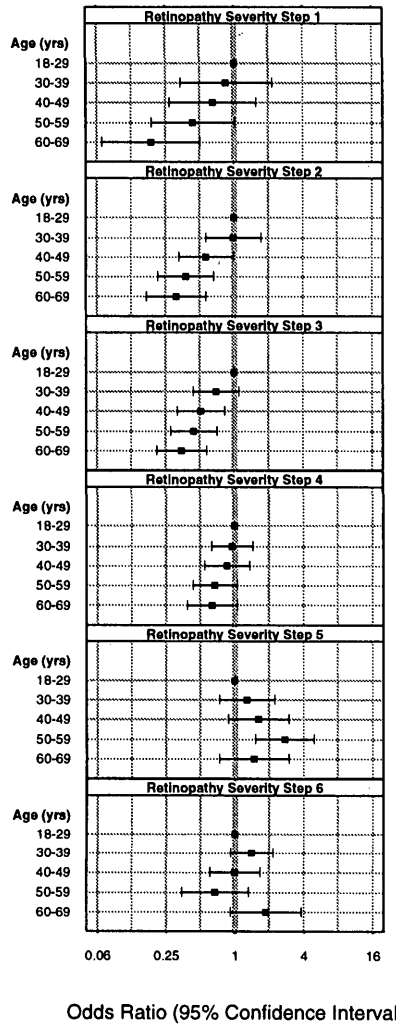

FIGURE 3. Odds ratio for developing high-risk PDR over 5 years of follow-up by age category within retinopathy severity step (from the final model; see Table 6).

identical. The risk for developing high-risk PDR increased significantly with increasing HbA_{1c} and decreasing visual acuity. In these analyses, the highest quartile of HbA_{1c} was divided into its upper and lower halves to explore a wider range of values. The odds ratio in the highest category relative to the lowest was 2.0 in the initial model and 1.6 in the final model. The effect of HbA_{1c} was similar in each retinopathy severity step. When the initial 5-year model was repeated separately for steps 1 to 3 combined and for steps 4 to 6 combined, the odds ratios (95% CI) for the highest category versus the lowest were, respectively, 1.97 (1.59-2.43) and 1.87 (1.51-2.32). For visual acuity, the odds ratios were 1.4 in the 70- to 84-letter category (20/40 to 20/20 − 1) and approximately 1.7 to 1.8 in the small group with visual acuity <20/40. The significance of macular edema as a risk factor was borderline, but its effect became stronger when visual acuity was omitted from the model, and the odds ratio was 1.5 in the most severe category in each model. With increasing diabetes duration, there was an increase in risk that was of borderline significance. In comparison to the <10-year duration category, risk was increased approximately equally in each of the longer duration categories, with odds ratios of approximately 1.4. Within each of these longer duration groups, patients were distributed evenly by age, but in the <10-year duration group, 72% of patients were 50 years or older and only 10% were younger than 40 years (versus 44%-51% and 33%-39%, respectively, in each of the other three duration groups), suggesting that the borderline duration effect was a further reflection of the age effect. There was a nonsignificant trend for decreasing risk with increasing body weight. Odds ratios for these factors in the final 5-year model are shown graphically in Figure 5.

The effects of the additional 11 variables that were retained in the final 5-year model are summarized in Table 8 and Figure 6. Table 8 also provides *P* values (italicized) for the single addition of each of the 11 variables to the initial 5-year model. The most impressive risk factors were history of diabetic neuropathy (suspected or definite), decreased hematocrit, increased triglyceride, and decreased albumin. For each of these variables, the effect was nominally significant in the 2- and/or 5-year final model and when the variable was added alone to the 2- and/or 5-year initial model. In the 2-year model, hematocrit was a nominally significant risk factor ($P = 0.0013$; odds ratio for the lowest hematocrit category = 2.08; 95% CI 1.41-3.07) and increased fibrinogen was a risk factor of borderline significance ($P = 0.030$; odds ratio in the highest

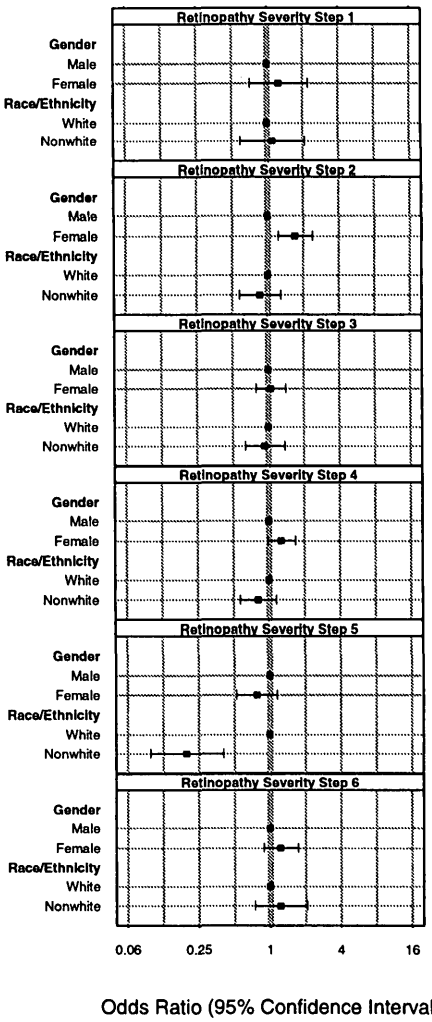

FIGURE 4. Odds ratio for developing high-risk PDR over 5 years of follow-up by gender and race-ethnicity categories within retinopathy severity step (from the final model; see Table 6).

TABLE 7. Initial and Final Models for Developing High-Risk Proliferative Diabetic Retinopathy during 5 Years of Follow-Up (Factors with Effects That Do Not Vary by Retinopathy Severity)

	*N**	*Initial Model OR† (95% CI‡)*	*Final Model OR† (95% CI‡)*
HbA_{1c}(%)			
<8.3	677	1.00	1.00
8.3-<9.6	627	1.04 (0.85-1.29)	0.97 (0.78-1.20)
9.6-<11.0	675	1.33 (1.09-1.62)	1.18 (0.96-1.46)
11-12	341	1.76 (1.40-2.21)	1.55 (1.22-1.96)
>12.0	334	1.96 (1.56-2.45)	1.59 (1.25-2.03)
P Value§		**<0.0001**	**<0.0001**
Type of Diabetes			
Strict I	819	1.00	1.00
Mixed	1009	1.08 (0.85-1.36)	1.09 (0.86-1.39)
Strict II	826	1.07 (0.76-1.52)	1.13 (0.79-1.63)
P Value§		0.83	0.76
Duration (years)			
<10	407	1.00	1.00
10-14	727	1.37 (1.07-1.74)	1.35 (1.06-1.72)
15-19	801	1.36 (1.06-1.74)	1.34 (1.04-1.72)
20+	719	1.38 (1.06-1.80)	1.41 (1.08-1.83)
P Value§		0.065	0.069
Desirable Weight (%)			
≤100	564	1.00	1.00
>100-120	1033	0.89 (0.75-1.06)	0.87 (0.73-1.03)
>120-140	595	0.90 (0.71-1.15)	0.83 (0.65-1.06)
>140	462	0.86 (0.66-1.12)	0.74 (0.56-0.98)
P Value§		0.55	0.16
Visual Acuity (no. of letters)			
85+	1302	1.00	1.00
70-84	1048	1.43 (1.15-1.77)	1.40 (1.20-1.63)
<70	304	1.80 (1.22-2.67)	1.67 (1.26-2.20)
P Value§		**0.0013**	**<0.0001**
Extent of Macular Edema			
None in Field 2	913	1.00	1.00
None in 1 DD of center	454	1.25 (1.03-1.51)	1.25 (1.03-1.52)
<1 DA in 1 DD of center	664	1.23 (1.02-1.48)	1.26 (1.04-1.52)
≥1 DA in 1 DD of center	623	1.18 (0.95-1.48)	1.19 (0.95-1.49)
P Value§		0.08	0.059
Extent of Macular Edema (Initial Model Excluding Visual Acuity)			
None in Field 2	913	1.00	1.00
None in 1 DD of center	454	1.27 (1.05-1.54)	1.27 (1.05-1.54)
<1 DA in 1 DD of center	664	1.31 (1.09-1.58)	1.34 (1.11-1.62)
≥1 DA in 1 DD of center	623	1.46 (1.19-1.78)	1.46 (1.19-1.79)
P Value§		**0.0017**	**0.0012**

PDR, proliferative diabetic retinopathy; DA, disc area; DD, disc diameter.

*Number of participants in each category at baseline.

†Odds ratio (OR) for developing high-risk PDR during 5 years of follow-up from the Cox discrete failure time model, which includes these main effects and retinopathy severity level, age, gender, and race/ethnicity, and the interactions between retinopathy severity level and age, retinopathy severity level and gender, and retinopathy severity level and race/ethnicity.

‡95% confidence interval (CI) for the given odds ratio.

§*P* value represents a test for difference in odds ratio across all levels of the given covariate.

fibrinogen category = 1.40; 95% CI 0.95-2.08). When fibrinogen was added alone to the initial 2-year model, the odds ratio in the highest category was 1.69 (95% CI 1.19-2.40). For the remaining variables in Table 8 and Figure 6, evidence of any effect was at best equivocal. Urine glucose was a nominally significant risk factor, but the odds ratios for each category suggest that the *P* values may be inflated (made smaller) by chance differences between categories, because there was no

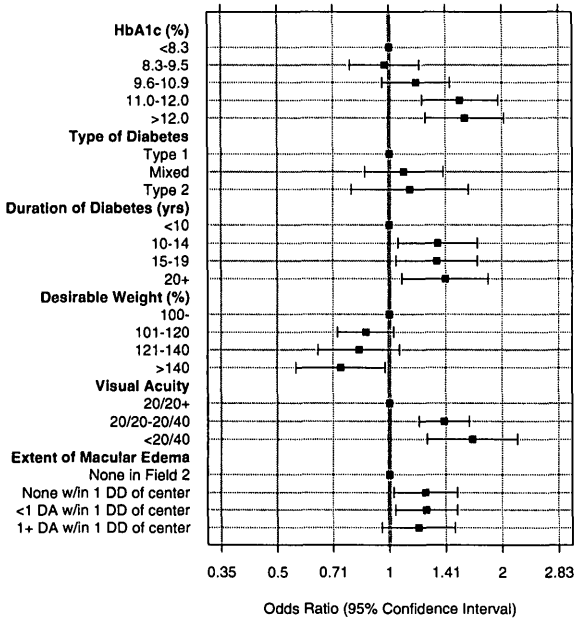

FIGURE 5. Odds ratio for developing high-risk proliferative diabetic retinopathy (PDR) within 5 years for other factors selected a priori (from the final model; see Table 7). DA, disc area; DD, disc diameter.

consistent trend in the odds ratios with increasing glucose. Cigarette smoking, history of coronary artery disease, and increased serum creatinine tended (at borderline significance levels) to reduce the risk for high-risk PDR. However, these are all risk factors for mortality as well, and we cannot adjust completely for this competing risk.

Figure 7 presents odds ratios for the single addition to the initial 5-year model of each of the 26 variables not included in the final models. Hard exudates, intraocular pressure, myopia, and blood pressure were not significant factors. Diminished vibratory sense in the feet was a nominally significant risk factor in the 5-year model and was of borderline significance in the 2-year model; presumably it was nonsignificant when added to the final models because of the neuropathy variable. Similarly, decreased pedal pulses, proteinuria, increased α_2-globulin, elevated total cholesterol, and low high-density-lipoprotein cholesterol were risk factors of borderline significance, and, a platelet count of <160,000 cells/mm^3 was a protective factor of borderline significance when these variables were added to the initial 2- and/or 5-year models.

Occurrence of Severe Visual Loss or Vitrectomy

Five-year cumulative incidence rates of SVLV and high-risk PDR are shown in Table 9. The first column of the table presents numbers at baseline, and the next three columns present cumulative 5-year rates of, respectively, SVLV occurring in eyes in which high-risk PDR had not (as yet) been observed, high-risk PDR, and SVLV occurring at or after the visit during which high-risk PDR was first observed. The last two columns of the table present numbers of eyes developing high-risk PDR and, among them, rates of SVLV 5 years after the visit during which high-risk PDR was first observed. The overall 5-year rate of SVLV occurring before high-risk PDR had been observed was 1.1% (27 of 2654). This rate tended to be higher in persons 50 years of age or older or in persons with type 2 or mixed categories of diabetes, in women, in white persons, and in persons in the highest categories of weight, visual acuity impairment, and macular edema. The overall 5-year rate of high-risk PDR was 38.4% (1005 of 2654), and that of SVLV occurring at or after high-risk PDR was 4.5% (119 of 2654). These rates increased 5-fold or more with increasing retinopathy severity and increased to a lesser extent with decreasing age, female gender, white race, increasing HbA_{1c}, type 1 diabetes, and duration of diabetes of ≥10 years. The overall 5-year rate of SVLV occurring at or after high-risk PDR among patients in whom high-risk PDR developed (without antecedent SVLV) was 15.8% (149 of 1146). This rate did not vary substantially across any of the above factors, indicating that development of high-risk PDR was the dominant risk factor. There were higher rates (approximately 20-25%), however, in the highest categories of weight, visual acuity impairment, and macular edema.

Risk Factors for SVLV

Table 10 presents odds ratios for the development of SVLV (with or without antecedent or concurrent high-risk PDR) at any time during follow-up. These were estimated using multivariable discrete Cox models that included the same 10 baseline variables selected for the initial high-risk PDR models and high-risk PDR as a time-dependent variable. The first column summarizes results of a model based on the 2654 patients with baseline laboratory data, and the second column shows similar results based on all 3680 patients. Development of high-risk PDR was the predominant risk factor, with odds ratios of 12 and 14. With this time-dependent factor included in the model, retinopathy severity and HbA1c were no longer significant. Baseline visual acuity, however, remained a significant factor. Odds ratios were approximately 1.5 and 2 or more, respectively, for visual acuity of 84 to 70 letters and of <70 letters. The odds ratio for weight >140% of desirable was 1.7 in both models, but this was of borderline significance and lesser degrees of overweight did not appear to have any effect. When the model was repeated without visual acuity, odds ratios for the most severe macular edema category were 1.7 to 1.8. A model in which history of diabetic neuropathy, hematocrit, trigylcerides, albumin, and fibrinogen were added gave similar results for all the factors in Table 10; hematocrit was of borderline significance in this model (P = 0.014; odds ratio for the lowest category = 1.88; 95% CI 1.25-2.84), as was albumin (P = 0.091; odds ratio for the lowest category = 1.59; 95% CI 1.02-2.48).

To test the significance of the trends shown in Table 9 for SVLV occurring without antecedent or concurrent high-risk PDR, univariate models were constructed in which SVLV of this type (41 cases occurring at any time during follow-up among all 3680 patients) was the dependent variable and the independent variables were those shown in Table 9 (except for HbA_{1c}). Older age, female gender, type 2 or mixed type diabetes, decreased visual acuity, and macular edema were all nominally significant risk factors, and increased body weight was of borderline significance.

DISCUSSION

Many studies have sought to identify factors associated with the presence, development, and/or progression of diabetic

TABLE 8. Final Model for Developing High-Risk Proliferative Diabetic Retinopathy (PDR) during 5 Years of Follow-Up (11 Additional Variables Included in the Final Model)

	*N**	*5-year OR*†	*(95% CI‡)*
History of Neuropathy			
No	1455	1.00	
Suspect	505	1.32	(1.10-1.57)
Definite	694	1.26	(1.07-1.48)
P Value§		**0.0019**	***0.0009***
Hematocrit (%)			
M < 40, F < 34	181	1.52	(1.14-2.04)
M 40-45, F 34-40	921	1.19	(1.02-1.39)
M > 45-50, F > 40-44	1122	1.00	
M > 50, F > 44	430	1.08	(0.89-1.32)
P Value§		0.019	***0.0038***
Triglycerides (mg/dl)			
not high	1814	1.00	
>140 18-29 yr, >150 30-39 yr >160 40-49 yr, >190 50-69 yr	837	1.23	(1.06-1.42)
P Value§		**0.0065**	***0.0049***
Albumin (g/dl)			
<3.0	383	1.35	(1.10-1.66)
3.0-<3.5	979	1.26	(1.07-1.47)
3.5-5.0	994	1.00	
P Value§		**0.0042**	***0.0016***
Fibrinogen (mg/dl)			
<165	43	1.29	(0.77-2.14)
165-275	1004	1.00	
>275-400	1069	1.10	(0.94-1.29)
>400	231	1.18	(0.89-1.56)
P Value§		0.46	*0.11*
Urine Glucose			
Negative	1080	1.00	
Trace	245	1.22	(0.96-1.55)
+	229	1.32	(1.03-1.70)
++	331	1.07	(0.86-1.34)
+++	454	1.45	(1.20-1.76)
++++	315	1.24	(0.99-1.55)
P Value§		**0.0045**	*0.025*
Cigarette Smoking			
Never	1286	1.00	
Former	618	1.02	(0.87-1.20)
Current <15 cigarettes/day	324	0.84	(0.68-1.04)
Current 15-25 cigarettes/day	244	0.82	(0.65-1.04)
Current >25 cigarettes/day	182	0.65	(0.48-0.87)
P Value§		0.017	0.092
History of Coronary Artery Disease			
No	2440	1.00	
Suspect	73	0.82	(0.52-1.28)
Definite	141	0.60	(0.41-0.88)
P Value§		0.027	*0.071*
Creatinine (mg/dl)			
<1.0	1000	1.00	
1.0-1.3	1350	0.85	(0.73-0.98)
>1.3	265	0.87	(0.61-1.13)
P Value§		0.082	*0.040*
Usual Consumption of Alcoholic Drinks			
Never	1580	1.00	
<1 day	891	1.17	(1.01-1.36)
≥1 day	183	1.05	(0.79-1.40)
P Value§		0.11	*0.23*
Current Arthritis (requiring medication)			
No	2355	1.00	
Suspect	158	1.13	(0.85-1.50)
Definite	141	1.23	(0.88-1.73)
P Value§		0.37	*0.58*

*Number of participants in each category at baseline.

†Odds ratio for developing high risk proliferative diabetic retinopathy during 5 years of follow-up from the Cox discrete failure time model, which includes these main effects; the main effects of HbA_{1c}; type and duration of diabetes; desirable weight (%); visual acuity and extent of macular edema; the main effects of retinopathy severity, age, gender and race/ethnicity; and the interactions between retinopathy severity and age, retinopathy severity and gender, and retinopathy severity and race/ethnicity.

‡95% confidence interval for the given odds ratio.

§*P* values are given for two different hypothesis tests. The *P* value in non-italic type represents a test for difference in odds ratio across all levels of the given covariate after adding all these 11 variables to the initial model. The *P* values in italics represent a test for difference in odds ratio across all levels of the given covariate after adding only that covariate to the initial model (using the Efron approximation to the likelihood). *P* values <0.01 are indicated in bold type.

retinopathy and with visual impairment resulting from it.[17-58] General agreement has evolved that duration of diabetes and severity of hyperglycemia are fundamental risk factors for the development of retinopathy. If retinopathy is present, duration of diabetes appears to be a less important factor for the progression from earlier to later stages of retinopathy, but the degree of hyperglycemia remains important as a risk factor for progression. There is less agreement across studies in regard to the importance of other factors, such as age, type of diabetes, blood pressure, blood lipids, and clotting factors.

Risk Factors for High-Risk Proliferative Diabetic Retinopathy

Retinopathy Severity at Study Entry. Retinopathy severity at study entry was the strongest factor in our analyses. This is not surprising for two reasons. First, the ETDRS retinopathy severity scale was described in a previous report[6] (and refined in this one) largely on the basis of its ability to predict the progression to PDR or high-risk PDR in the same group of patients as those analyzed in this report. Second, when the outcome of interest is progression to some specified level of severity rather than the progression of some specified amount along a severity scale that has more or less equal steps, it is obvious that baseline severity level will be important. An analogy is this: Persons beginning a race close to the designated finish line are likely to cross it sooner than those starting far from it. When the outcome of interest is development of severe NPDR, PDR, or high-risk PDR, adjusting for retinopathy severity at baseline is necessary if the goal is to identify risk factors for progression rather than factors associated with concurrent retinopathy severity. In this situation, the more complete the adjustment the better; thus our revision of the ETDRS scale (Tables 2, 3).

The importance of baseline retinopathy severity was evident early in the follow-up (Fig. 1), and the effect remained strong after controlling for other factors. Most odds ratios for step 6 versus step 1 were 9 or greater at 5 years (Tables 5, 6). Even for a more narrow range of the scale, step 1 (level 35)

versus step 3 (level 47), odds ratios ranged from 2 to 5 at 5 years.

Similar large effects, generally larger than those for any other risk factor, have been found across the lower part of similar scales in other prospective studies analyzing progression to PDR or high-risk PDR.[19-26,40] In the population-based Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR), in 708 insulin-dependent patients younger than 30 years of age at diagnosis of diabetes, the odds ratio for 4-year progression to PDR was 2.1 for each step increase in baseline retinopathy severity on an 11-step scale. This translates to a 40-fold greater risk for patients with baseline severity five steps higher than in the reference group, such as for example, for those with moderate NPDR in both eyes versus those with microaneurysms in only one eye.[21] Similar results were reported for risk of progression to PDR during the subsequent 6-year period for patients free of PDR at the 4-year visit, for those 30 years or older at diagnosis of diabetes, and for those younger than 30.[25] In a group of 322 patients with diagnosis of diabetes before age 17 years, the Pittsburgh Epidemiology of Diabetes Complications Study reported a 6-fold increase in the 2-year risk of PDR for each step on a 4-step retinopathy severity scale, equivalent to a 36-fold increase for patients with moderate to severe NPDR in one or both eyes versus those with microaneurysms only in one or both eyes.[26]

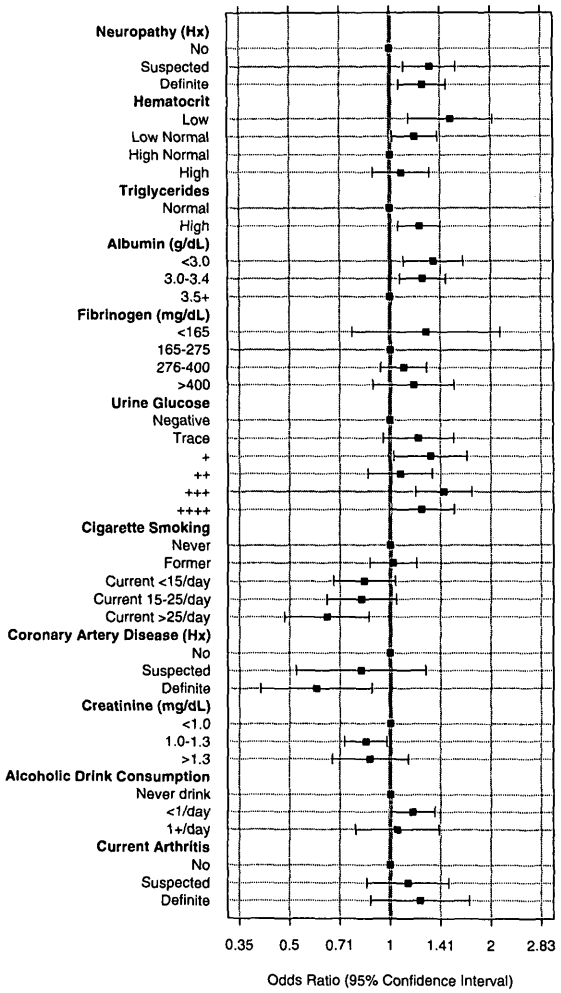

FIGURE 6. Odds ratios for developing high-risk PDR within 5 years for other factors remaining in the final model (Table 8).

Age and Diabetes Type. When considered separately, both younger age and type 1 diabetes (which are highly correlated) were risk factors for progression to high-risk PDR within retinopathy severity steps 1 to 3. In multivariate analyses, age was a stronger factor. Older age was associated with lesser risk for progression in steps 1 to 3, with odds ratios ranging from 0.19 to 0.44 at 5 years for persons 50 years of age or older compared with those 18 to 29 years of age (Table 6). This represents a 2- to 5-fold reduction in risk, but there was an increase in persons 30 to 40 years of age. There was a similar but weaker effect of age in step 4 but no consistent age effect in steps 5 or 6.

Most previous studies of risk factors for progression to severe retinopathy (severe NPDR, PDR, or high-risk PDR) have carried out separate analyses within diabetes type, with or without the inclusion of retinopathy severity, glycosylated hemoglobin, and/or other factors in multivariable analyses. Twofold decreases in the 4-year risk for progression to severe NPDR or PDR with 10-year age increments were found by Janka and coworkers[27] in patients with insulin-dependent diabetes (with an adjustment for baseline glycosylated hemoglobin) and by Nelson and coworkers[28] in Pima Indians with non-insulin-dependent diabetes. Our findings in steps 1 to 3 are consistent with these results. The WESDR found overall 4-year rates of progression to PDR of 11% (75 of 713), 7% (31 of 418), and 2% (11 of 486), respectively, in the three groups studied (persons younger than 30 at diagnosis and taking insulin, those 30 or older at diagnosis taking insulin, and those 30 or older at diagnosis not taking insulin), and 10-year rates of 30%, 24%, and 10%, respectively, in the three groups.[19,20,23] As expected, age increased and baseline retinopathy severity decreased across these three patient groups, but no comparisons were made that considered all these factors concurrently. In other WESDR analyses carried out within diabetes type adjusting for baseline retinopathy severity and glycosylated hemoglobin, younger age was a weak risk factor of borderline significance for progression to PDR within each diabetes type.[18,21,24]

Diabetes Duration. Diabetes duration was of borderline significance in the multivariable models, and only because risk was lower in patients with <10 years of known diabetes compared with those in each of the longer duration categories, all of which carried approximately equal risk (Table 7). Many studies have found an increasing prevalence or incidence of severe NPDR or PDR with increasing duration of diabetes (in some studies, only up to 15-20 years duration, after which rates remained the same or decreased).[19,20,23,26,28,29,32,33,44-47] However, when baseline retinopathy was carefully assessed and included in multivariate models (together with baseline glycosylated hemoglobin), duration of diabetes was usually no longer a risk factor for progression.[18,24,26] Thus diabetes duration is a determinant of retinopathy severity at any given time, but progression from any given severity level to PDR is determined mainly by that level (and other factors), regardless of the years over which that level was reached.

Gender and Race–Ethnicity. The increased risk for women versus men in retinopathy severity step 2 and the decreased risk in the nonwhite versus the white race-ethnicity category in step 5 were unexpected, unexplained, and perhaps a result of chance. Gender has been found to be of little or no importance in most other studies of progression to PDR,[19,20,23,26-28] particularly when baseline retinopathy sever-

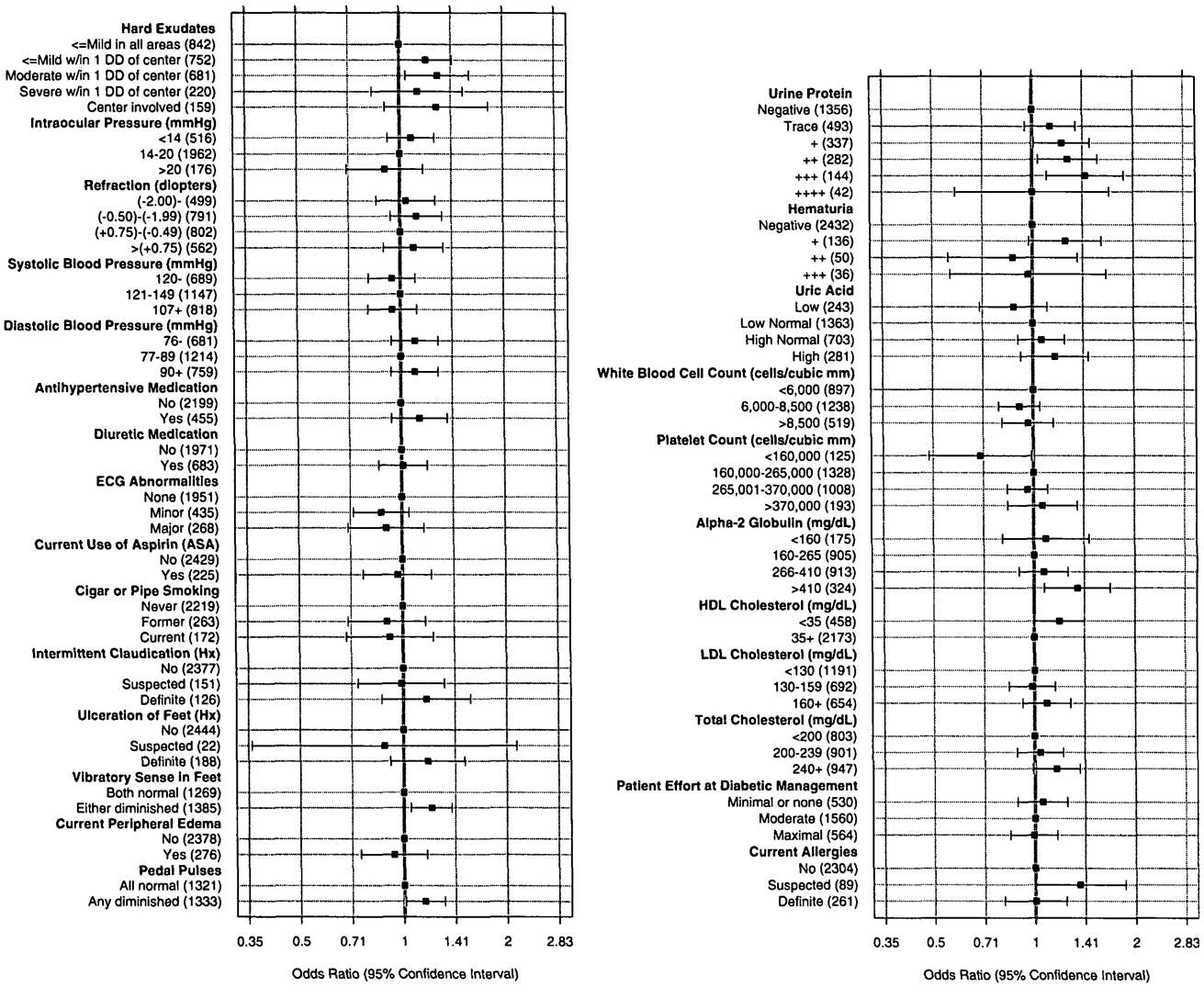

FIGURE 7. Odds ratio for developing high-risk PDR within 5 years for factors not included in the final model (odds are for each factor when added alone to the initial model).

ity and glycosylated hemoglobin were included in multivariate analyses.[18,24] There have been fewer studies of race-ethnicity as a risk factor for prevalence, incidence, or progression of diabetic retinopathy. In a cross-sectional study of patients in Southern Colorado with non-insulin-dependent diabetes, Hamman and coworkers[45] found duration-adjusted prevalence of retinopathy to be greater in non-Hispanic white than in Hispanic patients (54.1% versus 41.8%, $P = 0.04$). Glycosylated hemoglobin levels were similar in the two groups. In a similar study, Haffner and coworkers[32] reported the prevalence of retinopathy to be greater in Mexican Americans in San Antonio than in whites in Wisconsin. The possibility that greater exposure to hyperglycemia in the former group could explain the difference could not be examined because different measures were used. Arfken and coworkers[33] found the 4-year rate of 2-step or higher progression on the 11-step scale mentioned above to be greater for whites with insulin-dependent diabetes (43%) than for blacks (19%); in an analysis that adjusted for glycosylated hemoglobin, diabetes duration, and serum creatinine, the odds ratio was 2.62 (95% CI, 1.03-671). Few patients in either group progressed to PDR (4% of 142 and 2% of 58, respectively).

HbA_{1c}. In the final model, risk for progression to high-risk PDR increased by approximately 60% between the second and fourth quartiles of HbA_{1c}, which differed by approximately three percentage points (9% versus 12%, Table 7). Even in the lowest quartile of HbA_{1c}, the proportion of patients with progression was large (28% at 5 years, Table 9), and large odds ratios were not expected.

Degree of hyperglycemia has been found to be a strong risk factor for progression of retinopathy in observational studies[18,24,26,27,29-31,33,34] and clinical trials.[39-43] In a group of 1441 insulin-dependent patients assigned randomly to either conventional or intensive insulin treatment, the Diabetes Control and Complications Trial (DCCT) observed a reduction in the progression risk of approximately 35% to 40% for every 10% decrease (for example, from 8% to 7.2%) in HbA_{1c} (baseline and updated every 3 months during a follow-up period of 4 to 9 years), representing approximately a 5-fold increase in risk for patients with HbA_{1c} of approximately 10% versus those with 7%.[42] Over a 5- to 9-year follow-up period in a group of 102 insulin-dependent patients assigned randomly to conventional versus intensive insulin treatment, the Stockholm Diabetes Intervention Study[43] found (in a multivariate analysis that

TABLE 9. Cumulative 5-Year Incidence (%) of Severe Visual Loss or Vitrectomy and High-Risk Proliferative Diabetic Retinopathy

	No. at Baseline	*SVLV before or without HR-PDR**	*HR-PDR†*	*SVLV at or after HR-PDR‡*	*No. with HR-PDR*	*SVLV 5 Years after HR-PDR Visit§*
Total with HbA_{1c}	2654	1.1 (0.7-1.5)	38.4 (36.6-40.3)	4.5 (3.8-5.4)	1146	15.8 (13.6-18.4)
Retinopathy severity						
Step 1	416	1.0 (0.4-2.6)	13.9 (10.9-17.7)	0.7 (0.2-2.2)	69	14.0 (6.5-29.9)
Step 2	646	0.3 (0.1-1.2)	25.5 (22.4-29.2)	3.7 (2.5-5.5)	203	23.5 (16.6-33.3)
Step 3	660	1.4 (0.7-2.6)	34.7 (31.3-38.6)	3.0 (2.0-4.7)	270	14.8 (10.4-21.0)
Step 4	496	1.6 (0.8-3.2)	52.2 (47.9-56.8)	8.1 (6.0-10.9)	284	18.9 (14.4-24.6)
Step 5	191	1.0 (0.3-4.2)	66.0 (59.6-73.1)	4.2 (2.1-8.3)	131	7.7 (4.1-14.4)
Step 6	245	0.8 (0.2-3.2)	74.4 (69.1-80.1)	9.8 (6.7-14.3)	189	14.5 (10.1-20.7)
Age (years)						
18-29	450	0.4 (0.1-1.8)	54.7 (50.2-59.5)	8.9 (6.6-12.0)	271	19.7 (15.2-25.5)
30-39	391	0.8 (0.2-2.4)	50.4 (45.6-55.6)	5.4 (3.5-8.1)	215	13.4 (9.2-19.4)
40-49	440	0.7 (0.2-2.1)	40.9 (36.6-45.8)	5.2 (3.5-7.8)	210	14.7 (10.3-21.0)
50-59	753	1.4 (0.8-2.6)	31.9 (28.8-35.5)	2.5 (1.6-3.9)	280	16.1 (11.4-22.6)
60-69	620	1.3 (0.7-2.6)	25.2 (22.0-28.9)	2.6 (1.6-4.2)	170	14.7 (9.6-22.6)
Gender						
Male	1471	0.6 (0.3-1.2)	35.7 (33.3-38.3)	3.6 (2.8-4.7)	603	14.2 (11.3-17.7)
Female	1183	1.5 (1.0-2.4)	41.8 (39.0-44.7)	5.6 (4.4-7.1)	543	17.6 (14.3-21.6)
Race/ethnicity						
White	2077	1.2 (0.8-1.7)	40.4 (38.3-42.6)	4.9 (4.1-5.9)	944	15.8 (13.4-18.6)
Non-white	577	0.5 (0.2-1.6)	31.3 (27.7-35.4)	3.0 (1.8-4.7)	202	17.3 (11.4-26.2)
HBA_{1c}(%)						
<8.3	678	1.0 (0.5-2.2)	27.5 (24.3-31.1)	3.0 (1.9-4.5)	219	14.0 (9.6-20.4)
8.3-<9.6	626	1.3 (0.6-2.6)	34.1 (30.6-38.1)	4.2 (2.9-6.1)	237	18.1 (13.3-24.6)
9.6-<11.0	675	1.0 (0.5-2.2)	41.4 (37.8-45.3)	4.9 (3.5-6.8)	323	14.7 (10.9-19.8)
11.0-12.0	341	0.6 (0.1-2.3)	47.0 (41.9-52.6)	3.5 (2.0-6.1)	177	11.1 (6.8-17.9)
>12.0	334	0.9 (0.3-2.8)	53.6 (48.5-59.2)	8.3 (5.9-12.0)	190	21.2 (15.5-28.9)
Type						
Type 1	819	0.5 (0.2-1.3)	51.6 (48.2-55.1)	6.7 (5.2-8.7)	465	15.5 (12.3-19.5)
Mixed	1009	1.2 (0.7-2.1)	35.9 (33.0-39.0)	3.9 (2.8-5.3)	415	16.4 (12.6-21.1)
Type 2	826	1.3 (0.7-2.4)	28.5 (25.5-31.8)	3.0 (2.1-4.5)	266	16.0 (11.5-22.2)
Duration (years)						
<10	407	0.5 (0.1-2.0)	27.3 (23.2-32.0)	1.5 (0.7-3.3)	131	10.0 (5.3-18.8)
10-14	727	1.1 (0.6-2.2)	40.0 (36.6-43.8)	5.6 (4.2-7.6)	330	19.0 (14.8-24.5)
15-19	801	1.3 (0.8-2.5)	40.6 (37.3-44.1)	5.1 (3.8-6.9)	364	16.3 (12.5-21.3)
≥20	719	0.8 (0.4-1.9)	40.8 (37.3-44.6)	4.3 (3.1-6.1)	321	14.2 (10.5-19.2)
Weight, % desirable						
≤100	564	0.7 (0.3-1.9)	47.9 (44.0-52.3)	7.1 (5.2-9.6)	299	19.0 (14.7-24.8)
>100-120	1033	0.7 (0.3-1.4)	37.6 (34.7-40.7)	3.3 (2.4-4.6)	433	12.2 (9.2-16.4)
>120-140	595	1.2 (0.6-2.5)	34.3 (30.7-38.4)	2.9 (1.8-4.6)	231	10.2 (6.6-15.8)
>140	462	1.9 (1.0-3.7)	33.9 (29.8-38.5)	6.1 (4.2-8.7)	183	25.5 (19.2-33.8)
Visual acuity (no. of letters)						
85-100	1302	0.6 (0.3-1.2)	35.8 (33.3-38.5)	3.2 (2.4-4.4)	542	12.7 (9.9-16.3)
70-84	1048	1.1 (0.7-2.0)	42.1 (39.2-45.2)	5.7 (4.5-7.3)	486	17.2 (13.9-21.4)
<70	304	2.3 (1.1-4.8)	37.1 (32.0-43.0)	5.6 (3.5-8.9)	118	23.1 (15.6-34.2)
Extent of macular edema						
None	913	1.0 (0.5-1.9)	36.7 (33.7-40.0)	3.6 (2.6-5.1)	392	13.2 (10.0-17.4)
None within 1 DD of center	454	0.2 (0.0-1.6)	42.1 (37.7-46.9)	6.0 (4.1-8.6)	213	18.3 (13.3-25.2)
<1 DA within 1 DD of center	664	0.8 (0.3-1.8)	38.3 (34.7-42.2)	3.5 (2.3-5.2)	283	12.8 (8.9-18.3)
≥1 DA within 1 DD of center	623	1.9 (1.1-3.4)	38.4 (34.8-42.5)	5.8 (4.2-7.9)	258	20.7 (15.8-27.2)

*Estimates of crude cumulative incidence of severe visual loss or vitrectomy (SVLV) before or without the observation of high-risk proliferative diabetic retinopathy (PDR) after 5 years of follow-up from baseline and 95% confidence interval on the log(cumulative incidence) transformed back to the cumulative incidence scale.

†Estimates of crude cumulative incidence of high-risk PDR after 5 years of follow-up from baseline and 95% confidence interval on the log(cumulative incidence) transformed back to the cumulative incidence scale.

‡Estimates of crude cumulative incidence of SVLV at or after the observation of high-risk PDR after 5 years follow-up from baseline and 95% confidence interval on the log(cumulative incidence) transformed back to the cumulative incidence scale.

§Estimates of crude cumulative incidence of SVLV 5 years after the observation of high risk PDR and 95% confidence interval on the log(cumulative incidence) transformed back to the cumulative incidence scale.

DA, disc area; DD, disc diameter.

TABLE 10. Models for Severe Visual Loss or Vitrectomy during the Entire Follow-Up Period

	Total with HbA_{1c} (N = 2654)		*Total (N = 3680)*	
	*OR**	*(95% CI†)*	*OR**	*(95% CI†)*
High-risk PDR				
No	1.00		1.00	
Yes	11.7	(7.74-17.6)	13.7	(9.41-19.9)
P Value‡		**<0.0001**		**<0.0001**
Retinopathy severity step				
1	1.00		1.00	
2	1.18	(0.63-2.21)	1.30	(0.70-2.41)
3	0.95	(0.51-1.79)	1.22	(0.67-2.23)
4	1.25	(0.67-2.33)	1.46	(0.80-2.67)
5	0.54	(0.25-1.19)	0.69	(0.33-1.44)
6	0.66	(0.33-1.31)	0.86	(0.44-1.65)
P Value‡		**0.030**		**0.040**
Age (years)				
18-29	1.00		1.00	
30-39	0.71	(0.44-1.15)	0.70	(0.45-1.09)
40-49	0.63	(0.36-1.11)	0.63	(0.37-1.05)
50-59	0.49	(0.26-0.92)	0.49	(0.27-0.86)
60-69	0.54	(0.26-1.10)	0.60	(0.32-1.13)
P Value‡		0.27		0.15
Gender				
Male	1.00		1.00	
Female	1.19	(0.87-1.63)	1.18	(0.90-1.55)
P Value‡		0.28		0.24
Race/ethnicity				
White	1.00		1.00	
Nonwhite	0.71	(0.47-1.09)	0.81	(0.57-1.16)
P Value‡		0.12		0.25
HbA_{1c} (%)				
<8.3	1.00			NA
8.3-<9.6	1.25	(0.80-1.96)		NA
9.6-<11.0	1.01	(0.64-1.58)		NA
11.0-12.0	0.58	(0.33-1.05)		NA
>12.0	1.39	(0.86-2.25)		NA
P Value‡		**0.036**		
Type of Diabetes				
Strict 1	1.00		1.00	
Mixed	1.30	(0.74-2.28)	1.22	(0.73-2.02)
Strict 2	1.34	(0.60-3.01)	1.32	(0.64-2.72)
P Value‡		0.66		0.73
Duration (years)				
<10	1.00		1.00	
10-14	1.92	(1.06-3.46)	1.53	(0.95-2.48)
15-19	1.94	(1.06-3.57)	1.58	(0.96-2.57)
20+	1.80	(0.95-3.41)	1.48	(0.88-2.50)
P Value‡		0.16		0.31
Desirable Weight (%)				
≤100	1.00		1.00	
>100-120	0.74	(0.49-1.11)	0.97	(0.67-1.39)
>120-140	0.85	(0.48-1.50)	0.98	(0.59-1.63)
>140	1.70	(0.98-2.96)	1.71	(1.03-2.84)
P Value‡		**0.0021**		**0.027**

TABLE 10. (*continued*). Models for Severe Visual Loss or Vitrectomy during the Entire Follow-Up Period

	Total with HbA_{1c} (N = 2654)		*Total (N = 3680)*	
	*OR**	*(95% CI†)*	*OR**	*(95% CI†)*
Visual acuity (no. of letters)				
85+	1.00		1.00	
70-84	1.67	(1.17-2.38)	1.51	(1.10-2.06)
<70	2.54	(1.45-4.44)	2.05	(1.26-3.36)
P Value‡		**0.0021**		**0.0083**
Extent of macular edema				
None in field 2	1.00		1.00	
None within 1 DD of center	1.12	(0.72-1.74)	1.09	(0.73-1.64)
<1 DA within 1 DD of center	0.91	(0.58-1.41)	0.96	(0.66-1.42)
≥1 DA within 1 DD of center	1.23	(0.76-1.97)	1.34	(0.88-2.04)
P Value‡		0.59		0.39
Extent of macular edema (final model excluding visual acuity)				
None in field 2	1.00		1.00	
None within 1 DD of center	1.14	(0.73-1.78)	1.11	(0.74-1.67)
<1 DA within 1 DD of center	1.02	(0.66-1.56)	1.06	(0.72-1.55)
≥1 DA within 1 DD of center	1.72	(1.13-2.64)	1.75	(1.20-2.56)
P Value‡		**0.038**		**0.011**

PDR, proliferative diabetic retinopathy; DA, disc area; DD, disc diameter; NA, not applicable.

*Odds ratio (OR) for developing severe visual loss or vitrectomy over entire the follow-up period from the Cox discrete failure time model, which includes the time-dependent effect of development of high-risk PDR as well as the main effects of retinopathy severity step, age, gender, race/ethnicity, and other baseline characteristics included in the initial model.

†95% confidence interval (CI) for the given odds ratio.

‡*P* value represents a test for difference in odds ratio across all levels of the given covariate.

adjusted for baseline retinopathy severity) a 2.4-fold increase in the risk for serious retinopathy (PDR or macular edema requiring photocoagulation) for each percentage point increase in HbA_{1c} (for example, from 7% to 8%), representing approximately a 14-fold increase in risk for patients with HbA_{1c} of 10% versus those with 7%. In younger onset insulin-taking patients, the Pittsburgh and Wisconsin studies (mentioned above) found, respectively, 6- and 3-fold increases in the risk for PDR associated with a baseline glycosylated hemoglobin 3 percentage points higher.[18,26] In a subsequent WESDR analysis, HbA_{1c} was a significant predictor of the 10-year rate of PDR in all three patient groups studied, with odds ratios ranging from 1.5 to 1.9 for each percentage point of increase in baseline HbA_{1c} (representing 3- to 7-fold increases in risk with a 3-percentage-point increase in baseline HbA_{1c}).[24]

A question of considerable clinical importance is whether improved glycemic control has a beneficial effect on retinopathy even after it has progressed to the severe nonproliferative or early proliferative stage. Although the DCCT could not answer this question directly because those patients were ineligible, the beneficial effect of intensive treatment was observed in the most severe retinopathy subgroup included, which consisted of 70 patients with moderate NPDR.[40,49] Our finding that HbA_{1c} appeared to be of equal importance in models that included only eyes with severe NPDR or early PDR (steps 4-6)—as in models restricted to eyes with mild to moderate NPDR (steps 1-3)—suggests that the beneficial effect of improved control also applies to eyes in the former category. However, when initiation of intensive insulin treatment is considered for patients who have severe NPDR or early PDR and long-standing poor glycemic control, ophthalmologic monitoring is particularly important, because in such patients the risk for clinically important worsening of retinopathy in response to improved control appears to be substantial.[59,60] In such patients, photocoagulation of at least one eye before the initiation of intensive insulin treatment should be considered, and patients should be followed at 2- to 4-month intervals for at least 6 to 12 months after its initiation.

Visual Acuity. Reduced baseline visual acuity was a relatively strong risk factor for progression to high-risk PDR, even after adjustment for other factors, including extent of macular edema (an increase in risk of approximately 40% with a visual acuity score of 70 to 84 letters [20/40 to 20/20−1] and of approximately 75% with a score of <70 letters [worse than 20/40], Table 7). Apparently, reduced visual acuity reflects retinal damage predisposing to progression to high-risk PDR beyond that captured by the retinopathy severity and retinal thickening assessments.

We are not aware of other studies that have included visual acuity in risk factor analyses for development of PDR or high-risk PDR, but others have found baseline visual acuity to be an important risk factor for the development of severe degrees of visual loss. In the DRS, baseline visual acuity score (number of letters out of 100 read correctly) was the second variable selected, after severity of new vessels on or within 1 disc diameter of the disc margin, in multivariate analyses in which the outcome measures were the occurrence of visual acuity of either <5/200 or of ≤20/200 in eyes assigned to no treatment.[35] In the WESDR, baseline visual acuity was not examined in multivariate analyses, but, after 4 years of follow-up, visual acuity of ≤20/200 in the better eye had developed in approximately 25% of patients with baseline visual acuity in the better eye of 20/40 to 20/160, versus approximately 0.5% to 1.0% in those with visual acuity better than 20/40.[36]

Other Risk Factors. Four additional risk factors were nominally significant ($P < 0.01$) in the 2- and/or 5-year final models (history of diabetic neuropathy, decreased hematocrit, increased triglyceride, and decreased albumin), and one additional factor, increased fibrinogen, was of borderline significance in the 2-year final model only. All these characteristics have been identified in one or more previous studies as risk factors for the presence, severity, and/or progression of diabetic retinopathy.[34,35,37,38,48-58]

In a multivariate, cross-sectional analysis of approximately 2500 European patients with insulin-dependent diabetes, the risk for PDR (assessed in 45° fundus photographs, two fields in each eye) was approximately five times as great in persons with diabetic neuropathy as in those without it.[48] In a case-control study conducted at the Joslin Clinic, patients who had PDR after 15 to 21 years of insulin-dependent diabetes were compared with those who did not; in a multivariate model, the odds of having cardiovascular autonomic neuropathy were approximately 30- to 40-fold greater for those who had PDR than for those who did not. In this model the corresponding odds ratio for albumin excretion rate of ≥70 μg/minute versus <70/minute was approximately 3, as was the odds ratio for greater versus lesser hyperglycemia at clinic visits during the first 12 years of diabetes.[34] These authors emphasized that the relationship between cardiovascular autonomic neuropathy and PDR remained after adjusting for degrees of albuminuria and hyperglycemia and suggested that autonomic nervous system dysfunction, perhaps manifested by decreased responsiveness of the retinal vessels to autonomic humoral mediators, may be an independent factor in the pathogenesis of PDR. Consistent with this speculation was the finding in the DCCT that intensive insulin treatment appeared to reduce the risk for retinopathy progression to a lesser extent in the small group of patients who had diabetic neuropathy at baseline than in those who did not, but this was of borderline significance in an analysis not adjusted for other factors.[49] Moreover, most of the neuropathy that was observed in the DCCT was somatic rather than autonomic.[50] In our study, we could not separate somatic from autonomic neuropathy because history consistent with either type was recorded in a single item (as neuropathy absent, suspected, or definite). However, our finding that history of neuropathy remained a risk factor for the development of high-risk PDR in the final model is consistent with the notion that nervous system dysfunction caused by diabetes may be a pathogenetic factor in the progression of retinopathy.

Relatively little attention has been given to anemia as a possible risk factor for diabetic retinopathy. In the DRS analyses of baseline risk factors for subsequent development of visual loss mentioned above, decreased hematocrit was the second variable selected (after proteinuria) in a multivariate model that considered only nonocular factors, but it was not retained in a model that included retinopathy severity and visual acuity.[35] Two small case series have also suggested that anemia is a risk factor for diabetic retinopathy. The first was a report[56] of three patients whose retinopathy progressed from the mild nonproliferative stage to the florid proliferative stage concurrently with the development of severe anemia. The second was a report[57] of three patients in whom macular hard exudates decreased dramatically and visual acuity improved (in two of the three) after successful treatment of severe anemia with erythropoietin. A recent cross-sectional study[58] of patients attending a diabetes clinic in Finland found retinopathy to be twice as prevalent among 82 patients with hemoglobin levels of <12 g/dl as it was in 1304 patients with higher levels (44% versus 22%). When only those patients who had retinopathy were considered, retinopathy was classified as severe almost five times as frequently among those in the <12 g/dl hemoglobin category (53% versus 12%). In a multivariate analysis that included age, gender, duration and treatment of diabetes, fasting blood glucose, and presence of serum creatinine ≥ 115 μM/l and/or proteinuria, odds ratios comparing patients with <12 g/dl hemoglobin versus those with ≥12/g/dl hemoglobin were 2.0 (95% CI, 1.2-3.3) for presence of retinopathy and, among patients who had retinopathy, 5.3 (95% CI, 2.3-12.6) for severe retinopathy. Our finding of a progressive increase in risk for high-risk PDR with decreasing hematocrit in a model that adjusted for other risk factors adds substantially to the evidence supporting the importance of anemia as a risk factor for diabetic retinopathy (Table 8).

Previous ETDRS analyses found elevated serum lipids at baseline to be a risk factor for concurrent presence and subsequent development of retinal hard exudates, which were associated with decreased visual acuity.[13] The analyses reported here indicate that elevated lipids, most notably triglycerides, are also a risk factor for the development of high-risk PDR. This finding may provide additional motivation for lowering elevated lipid levels in patients with diabetic retinopathy.

Others have also reported associations between severe diabetic retinopathy and elevated triglyceride. In the cross-sectional analysis of European patients with insulin-dependent diabetes mentioned above, PDR was approximately twice as frequent among those in the highest triglyceride quartile versus those in the lowest, and this difference remained after adjustment for age, duration of diabetes, HbA_{1c}, diastolic blood pressure, and albuminuria.[51] A similar relationship was found for fibrinogen, but not for cholesterol. In a similar study in Pittsburgh, Kostraba and coworkers[52] also found elevated triglycerides, as well as elevated LDL cholesterol and fibrinogen, to be associated with the presence of PDR in a multivariate analysis, but the relationships weakened and became nonsignificant when the presence of overt diabetic nephropathy (defined as renal failure or albumin excretion rate of >200 g/minute) was included in the model. Weber and coworkers[53] also found an association between triglyceride level and the development of severe retinopathy. In the DCCT, in the conventional treatment group, the rate of retinopathy progression among patients in the highest quartile of baseline triglycerides was approximately twice that of those in the lowest quartile.[49] Increased fibrinogen and decreased albumin were found in a DCCT ancillary study to be associated with more frequent retinopathy progression.[54,55]

Validity of the Models. The models we used for the development of high-risk PDR assume constant hazard (odds) ratios over the entire follow-up time, an assumption that does not appear to be true for retinopathy severity (Fig. 1, Table 4). A comparison of the initial models for 2 and 5 years showed that the effect of retinopathy severity was stronger in the 2-year model ($P = 0.0011$). In the 2-year model, odds ratios for step 6 versus step 1 ranged from 15 to 193 across age, gender, and race-ethnicity categories (data not shown) versus a range of 6 to 52 in the 5-year model (Table 5). None of the other effects differed significantly between the two follow-up periods (for diabetes type, $P \geq 0.085$; for HbA_{1c}, $P = 0.12$). To control for the variable effect of retinopathy severity over time (that is, the variable hazard ratios), we examined discrete Cox models that were stratified by retinopathy severity. There were only minor

differences between the estimated effects from the original models and the estimated effects from the stratified models (data not shown).

Risk Factors for Severe Visual Loss or Vitrectomy

The predominant risk factor for SVLV was the development of high-risk PDR (odds ratio 12-14; Table 10). The only other clearly significant factor was decreased baseline visual acuity (odds ratios for visual acuity of <20/40 were approximately 2 to 2.5; Table 10). As mentioned above, multivariate risk factor analyses of the development of severe degrees of visual loss were also carried out in the DRS.[35] Findings were similar to ours in that retinopathy severity and visual acuity at baseline were the predominant risk factors.

Conclusion

The predominant risk factor for the progression of diabetic retinopathy to high-risk PDR was the severity of retinopathy at baseline. This finding underscores the importance of careful assessment of retinopathy severity in predicting prognosis clinically and in epidemiologic studies of other risk factors. In multivariate models that adjusted for retinopathy severity, other baseline risk factors were decreased visual acuity (or extent of macular edema if visual acuity was excluded from the model), higher glycosylated hemoglobin, history of diabetic neuropathy, lower hematocrit, elevated triglycerides, and lower serum albumin. In patients with mild to moderate NPDR at baseline, younger age was also a strong risk factor. The predominant risk factor for SVLV was development of high-risk PDR. The only other clearly significant factor was decreased baseline visual acuity.

Our findings support the view that the retinopathy-inhibiting effect of better glycemic control extends across all age groups, both diabetes types, and all degrees of retinopathy severity up to and including the severe nonproliferative and early proliferative stages. These findings also support the suggestion that the risk for retinopathy progression may be reduced by lowering elevated serum lipids[13] and by treating anemia.[56-58] The effect of age in patients with mild to moderate NPDR, which remained after adjustment for many other factors, suggests that some unmeasured variable closely associated with younger age, perhaps a growth factor, plays an important role in progression of retinopathy to the proliferative stage.

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