Fundus Photographic Risk Factors for Progression of Diabetic Retinopathy

ETDRS Report Number 12

EARLY TREATMENT DIABETIC RETINOPATHY STUDY RESEARCH GROUP*

Abstract: In the Early Treatment Diabetic Retinopathy Study, a randomized clinical trial sponsored by the National Eye Institute, one eye of each patient was assigned to early photocoagulation and the other to deferral of photocoagulation (i.e., careful follow-up and initiation of photocoagulation only if high-risk proliferative retinopathy developed). This design allowed observation of the natural course of diabetic retinopathy in the initially untreated eye. Gradings of baseline stereoscopic fundus photographs of eyes with nonproliferative retinopathy assigned to deferral of photocoagulation were used to examine the power of various abnormalities and combinations of abnormalities to predict progression to proliferative retinopathy in photographs taken at the 1-, 3-, and 5-year follow-up visits. Severity of intraretinal microvascular abnormalities, hemorrhages and/or microaneurysms, and venous beading were found to be the most important factors in predicting progression. On the basis of these analyses and other considerations, a retinopathy severity scale was developed. This scale, which divides diabetic retinopathy into 13 levels ranging from absence of retinopathy to severe vitreous hemorrhage, can be used to describe overall retinopathy severity and change in severity over time.
Ophthalmology 1991; 98:823–833

Like most other classifications of diabetic retinopathy,[1–3] the Early Treatment Diabetic Retinopathy Study (ETDRS) modification of the Airlie House classification[4] is limited to assessing the severity and/or extent of various characteristic abnormalities; it does not provide an overall severity scale. In the Diabetic Retinopathy Study (DRS), a useful definition was proposed for one part of such a scale, the *severe* stage of nonproliferative diabetic retinopathy (NPDR). In this definition, which was based on clinical impression and qualitative clinical descriptions,[5–9] four abnormalities were considered: hemorrhages and/or microaneurysms, cotton–wool spots (soft exudates), intraretinal microvascular abnormalities (IRMAs), and venous beading, as shown in Table 1.[10]

To be eligible for entry into the DRS, patients who did not have new vessels in at least one eye were required to have severe NPDR in each eye. Analyses of the course followed by eyes assigned to the untreated control group in the DRS showed that approximately 50% of eyes without new vessels (a group drawn approximately equally from patients with severe NPDR in both eyes and from patients with new vessels limited to the eye assigned to treatment, whose untreated eye in some cases had NPDR less than severe) progressed to proliferative diabetic reti-

Originally received: July 19, 1990.
Revision accepted: January 24, 1991.

* A list of the ETDRS Research Group Investigators appears at the end of ETDRS report number 7 in this supplement to *Ophthalmology*.

Presented in part at the American Academy of Ophthalmology Annual Meeting, New Orleans, Oct/Nov 1989.

Reprint requests to the Biometry and Epidemiology Program, National Eye Institute, Bldg 31, Room 6A-24, 9000 Rockville Pike, Bethesda, MD 20892.

Table 1. Severe Nonproliferative Diabetic Retinopathy*

Either of the Following	
Presence of any three P2 characteristics	P2 characteristics
	SE ≥ definitely present in ≥ 2 of photographic fields 4 to 7
	IRMA ≥ definitely present in ≥ 2 of photographic fields 4 to 7
	VB ≥ definitely present in ≥ 2 of photographic fields 4 to 7
	H/Ma ≥ severe (≥ std photo 2A) in ≥ 1 of photographic fields 4 to 7
IRMA ≥ moderate (≥ standard photo 8A) in ≥ 2 of photographic fields 4 to 7 and ≥ definitely present in the remaining 2 fields	

SE = soft exudates (cotton-wool spots); IRMA = intraretinal microvascular abnormalities (dilated pre-existing vessels or intraretinal new vessles); VB = venous beading (in the DRS included with other venous caliber abnormalities); H/Ma = hemorrhages and/or microaneurysms; standard photo = standard photographs of modified Airlie House classification.[4,10]

* Designated group 3 in the DRS and group P2 in the ETDRS. This definition is slightly modified from that given in the DRS manual of operations but is virtually equivalent.

nopathy (PDR) over a period of approximately 15 months.[11]

Additional DRS analyses suggested that hemorrhages and/or microaneurysms and venous beading were more powerful predictors of visual loss than were soft exudates and IRMAs, and also found the severity of arteriolar abnormalities to have some predictive power.[12,13] The DRS provided support for previous observations that identified new vessels on the optic disc[14] and vitreous or preretinal hemorrhage as risk factors for visual loss. On the basis of location and severity of new vessels and presence of vitreous or preretinal hemorrhage, the DRS divided PDR into two subgroups (here termed "early PDR" and "high-risk PDR").[15] Klein and co-workers[16] proposed a scale of overall retinopathy severity that divided NPDR into four levels, the most severe of which (their level 5) was identical to the severe NPDR group of the DRS. The Kroc Study used this scale and suggested subdivisions for it, but small numbers of patients and a short follow-up period precluded assessment of the prognostic value of the expanded scale.[17]

The ETDRS adopted the DRS definitions of severe NPDR and high-risk PDR and defined moderate NPDR (group P1) as the presence of one or more of the four abnormalities considered in the definition of severe NPDR: soft exudates, IRMAs, venous beading, and severe hemorrhages and/or microaneurysms. Subsequently, the ETDRS developed a more detailed scale, designated the interim scale, which provided further subdivisions within both the NPDR and PDR categories. As follow-up information became available, the course of retinopathy in eyes assigned to deferral of photocoagulation provided an opportunity to test the prognostic power of that part of the interim scale represented in ETDRS patients at enrollment and, if it seemed desirable, to modify it. This report presents the results of such an investigation, describes the modified (final) scale, and assesses its reproducibility. Because the interim scale is being used in several other studies, the part of it that was modified is described in the appendix, where comparisons also are made between the two versions.

METHODS

From April 1980 to July 1985, the ETDRS enrolled 3711 diabetic patients who had diabetic retinopathy in both eyes. Each eye had to meet either of the following definitions: (1) moderate or severe NPDR or early PDR, absence of macular edema, and visual acuity of 20/40 or better; (2) any degree of NPDR (including microaneurysms only) or early PDR, presence of macular edema, and visual acuity of 20/200 or better. For eligibility purposes, macular edema was defined from gradings of stereoscopic color and fluorescein photographs as either (1) retinal thickening within 1 disc diameter of the center of the macula, or (2) hard exudates within a 30° photographic field centered on the macula (field 2) equaling or exceeding those in standard photograph 3,[4,10] with some of these hard exudates within 1 disc diameter of the center of the macula. Details of study design, including more complete eligibility requirements, have been published previously.[18]

Patients were randomly assigned to take either aspirin (650 mg once daily) or a placebo. One eye of each patient was randomly assigned to early photocoagulation and the other to deferral of photocoagulation (i.e., careful follow-up with initiation of photocoagulation only if high-risk PDR developed). The eyes assigned to deferral afforded the opportunity to investigate the course of nonproliferative and early proliferative retinopathy in the absence of photocoagulation. Beginning late in 1985, when the ETDRS reported the efficacy of focal photocoagulation for clinically significant macular edema,[19] eyes in the deferral group with clinically significant macular edema were considered for such treatment, but scatter treatment was not performed unless high-risk PDR developed.

Nonsimultaneous stereoscopic 30° color photographs were taken of seven standard fields at baseline, 4 months, and 1 year after entry, and yearly thereafter. The baseline photographs were typically obtained 2 to 3 months before actual entry into the study, so that the period between the baseline and 1-year photographs was usually 14 to 15 months.

Photograph sets were graded as previously described.[4] The grades for each characteristic for each photographic field were entered into a computerized file using the Wisconsin Information Storage and Retrieval System (WISAR) and were edited for completeness and internal consistency. For each characteristic graded in more than one photographic field, the individual grades were combined into a summary grade as previously described.[4] Further processing and statistical analyses (except for

stepwise logistic regression) were performed using the Statistical Analysis System (SAS). Regression analyses were performed using BMDP Biomedical Computer Programs.

To test and possibly modify that part of the interim scale represented in ETDRS patients at enrollment, the Reading Center chose a sample of 1959 patients who had entered the study during the initial 3 years of recruitment, whose 1-year visit photograph grading had been completed, and whose eye assigned to deferral had had NPDR at baseline. Another sample of 836 subsequently enrolled patients with NPDR at baseline in the eye assigned to deferral and with 1-year photograph gradings available was reserved for validation of the final scale. Since the Reading Center was masked to drug treatment assignment, patients from both the aspirin and placebo groups were included.

One of the duplicate gradings of the baseline photographs of each of these eyes was selected randomly and used to construct tabulations of progression to PDR at the 1-year visit by baseline severity of individual characteristics and by overall retinopathy severity according to the interim scale. Proliferative diabetic retinopathy at the 1-year visit was defined as the presence in the photographs of definite new vessels or fibrous proliferations, definite vitreous or preretinal hemorrhage, or scars from scatter photocoagulation, which indicated the previous occurrence of high-risk PDR. Available gradings from the 3- and 5-year visits were used for similar tables.

Inspection of the tables using the interim scale showed obvious deficiencies, such as less prognostic importance for soft exudates than had been assumed when the scale was designed, and less importance than seemed appropriate on the basis of the tables for individual characteristics. The definitions of levels of NPDR in the interim scale were therefore revised, with the goal of producing a hierarchy of levels that (1) differed substantially from each other in prognosis for development of PDR, (2) grouped eyes with similar prognosis together, (3) were of reasonable size, and (4) had relatively simple definitions. This process went through several iterations.

After this process was completed, univariate and multivariate logistic regression models were constructed using PDR at the 1-, 3-, and 5-year visits as the dependent variable and baseline photographic gradings as independent variables. The risk factors identified by these two approaches were then compared. Using the final scale, rates of progression to PDR for the reserved sample of 836 eyes were compared with those for the original sample.

For the regression analyses, entropy[20] was used to estimate the association of sets of independent variables with the dependent variable (outcome measure). Entropy is a function of the logarithm of the likelihood ratio of a model using independent variables as predictors compared with a model with no independent variables. To assess the importance of variables in the logistic regression, it is calculated sequentially as variables are added to the model. The importance of a variable is estimated by the increase in entropy occurring when that variable is added to the model. It has been suggested that entropy is analogous to R^2 in multiple linear regression; the higher its value, the greater the association.[20]

Reproducibility of the scale was assessed by calculating percentages of varying degrees of agreement for two independent gradings, and by calculating unweighted and weighted kappa statistics.

Table 2. Percent of Eyes With Progression to Proliferative Diabetic Retinopathy at 1-, 3-, and 5-Year Visits by Severity of Hemorrhages/Microaneurysms in Baseline Fundus Photographs

	1-Year Follow-up		3-Year Follow-up		5-Year Follow-up	
Grade*	Percent	No.†	Percent	No.†	Percent	No.†
D/1	0	2	0	2	0	1
D/2–3	0	12	30.0	10	28.6	7
D/4–5	10.1	158	24.1	145	36.8	125
M/1	9.1	175	22.5	160	37.8	127
M/2–3	14.4	362	30.3	327	41.1	265
M/4–5	21.1	693	40.8	618	57.2	505
S/1	30.7	261	44.8	232	65.3	190
S/2–3	40.7	167	67.1	143	75.9	112
S/4–5	49.0	51	66.7	42	82.8	29
VS/1	46.9	49	69.8	43	83.8	37
VS/2–5	72.4	29	80.0	25	85.0	20
Total	22.8	1959	40.2	1747	54.7	1418

* Severity categories for characteristics graded in multiple fields are of the form (maximum severity/extent), where maximum severity can be absent (A), questionable (Q), definitely present (D), moderate (M), severe (S), or very severe (VS), and extent is the number of fields at that severity level. For example, M/2–3 means there are two or three fields from fields 3 to 7 with moderate severity, and none with higher severity.

† Number at risk.

RESULTS

Tables 2 through 6 examine the relationship between baseline severity of hemorrhages and/or microaneurysms, IRMAs, venous beading, soft exudates, and hard exudates and the rate of progression to PDR at the 1-, 3-, and 5-year follow-up visits. One-year progression rates increased fourfold or more with increasing severity of hemorrhages and/or microaneurysms, IRMAs, and venous beading; they doubled with increasing severity of soft exudates. There appeared to be little or no relationship between severity of hard exudates and risk of PDR. The presence of venous beading (grade D/1 or greater) was a more powerful predictor of the subsequent development of PDR than was the presence of any other abnormality.

The other characteristics of retinal veins that were graded (loops/reduplication, narrowing, sheathing, perivenous exudate) occurred infrequently; none of these abnormalities was present at any level of severity in as many as 25% of eyes. There did not appear to be a strong relationship between baseline severity and the development of PDR for any of these characteristics. Arteriolar sheathing and arteriovenous nicking also were infrequent and not strongly related to development of PDR. Arteriolar

Table 3. Percent of Eyes with Progression to Proliferative Diabetic Retinopathy at 1-, 3-, and 5-Year Visits by Severity of Intraretinal Microvascular Abnormalities (IRMA) in Baseline Fundus Photographs

	1-Year Follow-up		3-Year Follow-up		5-Year Follow-up	
Grade*	Percent	No.†	Percent	No.†	Percent	No.†
A	9.3	421	21.2	378	36.9	293
Q/1	12.4	153	30.4	138	37.7	106
Q/2–3	12.1	165	27.5	142	36.2	105
Q/4–5	14.7	109	24.2	99	39.5	76
D/1	22.0	382	42.7	337	58.5	270
D/2–3	29.0	411	50.3	370	64.7	314
D/4–5	39.6	177	61.9	160	75.7	140
M/1	54.9	82	71.4	70	79.4	63
M/2–3	60.0	40	68.6	35	85.3	34
M/4–5	83.3	6	83.3	6	100.0	6
S/1	44.4	9	87.5	8	62.5	8
S/2–5	50.0	4	75.0	4	66.7	3
Cannot grade	0.0	1		0		0
Total	22.8	1959	40.2	1747	54.7	1418

* Severity categories for characteristics graded in multiple fields are of the form (maximum severity/extent), where maximum severity can be absent (A), questionable (Q), definitely present (D), moderate (M), severe (S), or very severe (VS), and extent is the number of fields at that severity level. For example, M/2–3 means there are two or three fields from fields 3 to 7 with moderate severity, and none with higher severity.

† Number at risk.

Table 4. Percent of Eyes with Progression to Proliferative Diabetic Retinopathy at 1-, 3-, and 5-Year Visits by Severity of Venous Beading in Baseline Fundus Photographs

	1-Year Follow-up		3-Year Follow-up		5-Year Follow-up	
Grade*	Percent	No.†	Percent	No.†	Percent	No.†
A	15.4	1072	32.4	952	47.3	771
Q/1	16.2	284	35.9	265	49.1	220
Q/2–3	26.0	235	43.9	212	60.4	159
Q/4–5	41.3	63	60.8	51	72.7	44
D/1	40.5	168	58.1	148	75.0	124
D/2–3	52.0	98	73.3	86	77.8	72
D/4–5	83.3	24	84.2	19	94.4	18
M	66.7	15	78.6	14	80.0	10
Total	22.8	1959	40.2	1747	54.7	1418

* Severity categories for characteristics graded in multiple fields are of the form (maximum severity/extent), where maximum severity can be absent (A), questionable (Q), definitely present (D), moderate (M), severe (S), or very severe (VS), and extent is the number of fields at that severity level. For example, D/2–3 means there are two or three fields from fields 3 to 7 with definite presence of the characteristic, and none with higher severity.

† Number at risk.

Table 5. Percent of Eyes with Progression to Proliferative Diabetic Retinopathy at 1-, 3-, and 5-Year Visits by Severity of Soft Exudates in Baseline Fundus Photographs

	1-Year Follow-up		3-Year Follow-up		5-Year Follow-up	
Grade*	Percent	No.†	Percent	No.†	Percent	No.†
A	15.5	129	25.4	118	37.6	93
Q/1	19.1	84	29.0	76	44.3	61
Q/2–3	14.8	61	24.5	53	30.2	43
Q/4–5	9.1	22	25.0	20	25.0	16
D/1	19.4	315	33.0	282	40.6	229
D/2–3	21.3	427	40.1	384	52.9	314
D/4–5	27.4	223	46.7	199	63.1	157
M/1	21.8	289	40.0	260	60.1	208
M/2–3	24.7	194	47.1	172	65.8	146
M/4–5	42.2	45	61.0	41	80.7	31
S/1	32.4	111	53.2	94	70.1	77
S/2–3	37.0	54	65.1	43	86.8	38
S/4–5	20.0	5	80.0	5	100.0	5
Total	22.8	1959	40.2	1747	54.7	1418

* Severity categories for characteristics graded in multiple fields are of the form (maximum severity/extent), where maximum severity can be absent (A), questionable (Q), definitely present (D), moderate (M), severe (S), or very severe (VS), and extent is the number of fields at that severity level. For example, M/2–3 means there are two or three fields from fields 3 to 7 with moderate severity, and none with higher severity.

† Number at risk.

Table 6. Percent of Eyes with Progression to Proliferative Diabetic Retinopathy at 1-, 3-, and 5-Year Visits by Severity of Hard Exudates in Baseline Fundus Photographs

	1-Year Follow-up		3-Year Follow-up		5-Year Follow-up	
Grade*	Percent	No.†	Percent	No.†	Percent	No.†
A	19.2	104	30.8	91	40.9	71
Q/1	28.3	53	36.7	49	53.9	39
Q/2–3	24.0	50	30.4	46	47.4	38
Q/4–5	30.0	30	55.6	27	62.5	24
D/1	24.5	143	35.4	130	48.6	109
D/2–3	22.0	191	36.6	175	54.4	138
D/4–5	30.3	33	50.0	32	57.1	28
M/1	22.2	297	38.0	258	55.2	221
M/2–3	24.5	253	45.1	233	61.6	185
M/4–5	24.2	33	53.3	30	65.4	26
S/1	19.0	353	43.5	308	51.5	237
S/2–3	27.4	252	42.0	226	59.8	184
S/4–5	15.8	19	35.7	14	57.1	14
VS/1	19.4	124	39.3	107	53.2	88
VS/2–3	23.8	21	38.9	18	53.3	15
VS/4–5	0.0	3	0.0	3	100.0	1
Total	22.8	1959	40.2	1747	54.7	1418

* Severity categories for characteristics graded in multiple fields are of the form (maximum severity/extent), where maximum severity can be absent (A), questionable (Q), definitely present (D), moderate (M), severe (S), or very severe (VS), and extent is the number of fields at that severity level. For example, M/2–3 means there are two or three fields from fields 3 to 7 with moderate severity, and none with higher severity.

† Number at risk.

Table 7. Percent of Eyes with Progression to Proliferative Diabetic Retinopathy at the 1-, 3-, and 5-Year Visits, by Baseline Retinopathy Severity Level,* Final Scale

Baseline Retinopathy Severity Level and Component Definitions	1-Year Follow-up		3-Year Follow-up		5-Year Follow-up	
	Percent	No.†	Percent	No.†	Percent	No.†
Level 35						
A. Venous loops ≥ D/1	0.0	2	0.0	2	50.0	2
B. SE, IRMA, or VB = Q		0		0		0
C. RH present	5.0	20	10.5	19	6.3	16
D. HE = D/1–5	5.3	19	11.1	18	42.9	14
E. HE ≥ M/1	5.5	91	16.3	86	21.4	70
F. SE ≥ D/1	4.1	243	14.4	216	26.7	161
Level 35 total	4.5	375	14.4	341	25.1	263
Level 43						
A. H/Ma = M/4–5-S/1	10.5	354	24.8	315	40.7	248
B. IRMA = D/1–3	15.0	234	37.0	208	49.2	179
Level 43 total	12.2	588	29.6	523	44.3	427
Level 47						
A. Both L43 definitions	21.7	323	43.6	289	63.8	235
B. IRMA = D/4–5	28.3	99	52.2	90	70.4	81
C. H/Ma = S2–3	30.2	96	55.3	85	65.6	64
D. VB = D/1	34.5	87	48.8	82	71.9	64
Level 47 total	26.0	605	47.6	546	66.4	444
Level 53						
A. ≥2 L47 definitions	44.0	50	72.1	43	76.9	39
B. H/Ma ≥ S/4–5	47.9	96	67.1	79	80.7	57
C. IRMA ≥ M/1	44.2	95	64.7	85	75.3	77
D. VB ≥ D/2–3	51.1	88	73.7	76	76.3	59
E. ≥2 L53 definitions	75.4	61	83.0	53	90.2	51
Level 53 total	51.5	390	71.1	336	79.5	283
Total overall	22.8	1958‡	40.3	1746‡	54.7	1417‡

SE = soft exudates; IRMA = intraretinal microvascular abnormalities; VB = venous beading; RH = retinal hemorrhages; HE = hard exudates; H/Ma = hemorrhages/microaneurysms.

* Severity categories for characteristics graded in multiple fields are of the form (maximum severity/extent), where maximum severity can be absent (A), questionable (Q), definitely present (D), moderate (M), severe (S), or very severe (VS), and extent is the number of fields at that severity level. For example, M/2–3 means there are two or three fields from fields 3 to 7 with moderate severity, and none with higher severity.

† Number at risk.

‡ Excludes one eye classified by preliminary grading into level 35 but by detailed grading into level 20.

narrowing was at least questionably present in more than 50% of eyes, but was of moderate or greater severity in less than 10% of eyes; it appeared to be somewhat less strongly related to development of PDR than were soft exudates. The various characteristics of retinal thickening graded in field 2 did not appear to be related to development of PDR.

Detailed information on the segment of the final scale dealing with mild-to-severe NPDR is presented in Table 7, which provides 1-, 3-, and 5-year rates of PDR for eyes with NPDR at baseline. The overall rate for each level is given, as are the rates for each of the components of its definition. Eyes are classified in a given level when any of its component definitions is met, provided that the definition of any higher level is *not* met. In Table 7, within each level an eye is placed in the highest of the component definitions for which it qualifies. For example, in level 35, eyes that have both hard exudates and soft exudates (but no abnormality qualifying them for a higher level) are placed in category 35F, since it is the highest of the level 35 definitions for which such eyes could qualify. This scale divides eyes with mild-to-severe NPDR into four levels, each containing approximately 20 to 30% of the patients enrolled in the ETDRS. The range of progression rates for the categories included within each level is relatively narrow and the differences between levels are substantial. For each one-level increase on the scale, the 1-year rate of progression to PDR approximately doubles, increasing from 4.1% for level 35 to 12.2% for level 43, 26.0% for level 47, and 51.5% for level 53. Results after 3 and 5 years of follow-up were similar.

Table 8 presents the results of forward stepwise logistic

Table 8. Forward Stepwise Logistic Regression for Progression to Proliferative Diabetic Retinopathy at Specified Follow-up Visits Using Baseline Characteristics as the Independent Variables*

Visit	Characteristic	Beta	Standard Error	*P*-Value	Entropy
1-Year (n = 1959)	IRMA	0.232	0.031	0.0001	0.085
	H/Ma	0.389	0.042	0.0001	0.135
	VB	0.211	0.034	0.0001	0.155
	VS	0.347	0.102	0.0009	0.160
	HE	−0.057	0.018	0.0018	0.165
	VLR	0.151	0.051	0.0032	0.169
	SE	−0.063	0.026	0.0130	0.172
3-Year (n = 1747)	H/Ma	0.306	0.039	0.0001	0.056
	IRMA	0.209	0.026	0.0001	0.110
	VB	0.161	0.034	0.0001	0.119
	VLR	0.136	0.053	0.0090	0.122
	FTSZ	−0.205	0.053	0.0001	0.124
	MCTK	0.414	0.161	0.0096	0.127
	HE	0.046	0.022	0.0355	0.129
5-Year (n = 1418)	IRMA	0.182	0.027	0.0001	0.067
	H/Ma	0.270	0.045	0.0001	0.104
	VB	0.136	0.040	0.0005	0.110
	SE	0.081	0.025	0.0010	0.115
	PVEX	0.273	0.115	0.0109	0.118
	FTSZ	−0.069	0.031	0.0233	0.120

IRMA = intraretinal microvascular abnormalities; H/Ma = hemorrhages and/or microaneurysms; VB = venous beading; VS = venous sheathing; HE = hard exudates; VLR = venous loops/reduplication; SE = soft exudates; FTSZ = extent size of retinal thickening within all of field 2; MCTK = maximum thickness of the retina within 1500 μm of the center of the macula; PVEX = perivenous exudate.

* Entry into model stopped at 0.05 significance level.

regression models for each follow-up period, using baseline characteristics as the independent variables and progression to PDR as the dependent variable. Intraretinal microvascular abnormalities, hemorrhages and/or microaneurysms, and venous beading were the first three variables selected in each model. Venous sheathing, venous loops/reduplications, and perivenous exudate also contributed slightly to the models. Hard exudates and soft exudates showed weak inverse relationships to progression to PDR in the 1-year model, and soft exudates showed a weak direct correlation in the 5-year model. Weak inverse relationships also were present for extent of retinal thickening in field 2 in the 3- and 5-year models, and there was a weak direct correlation for maximum thickness of the retina within 1500 μm of the center of the macula in the 3-year model. In corresponding univariate logistic regressions with PDR at the 1-year visit as the dependent variable, IRMAs, hemorrhages and/or microaneurysms, and venous beading had similar beta coefficients (0.32, 0.40, and 0.38, respectively) and entropy measures (0.085, 0.074, and 0.078, respectively). The lesions with the next largest entropy measures in univariate regressions were venous loops/reduplications (0.013) and soft exudates (0.011).

Rates of PDR at 1 and 3 years among the patients whose gradings were used to develop the final scale were compared with rates observed in patients entering the study during the remainder of the recruitment period. In this later group, there were 836 patients with completed photograph gradings from the 1-year follow-up visit and 797 with gradings from the 3-year visit. For each level of the final scale, the 1- and 3-year rates in the earlier and later enrollment groups were within 3 percentage points of each other, except for a 5.3 percentage point difference for level 53 at 1 year (51.5% of 390 patients enrolling in the earlier period versus 46.2% of 132 patients enrolling in the later period). Only 103 patients who entered the study during the later period had had 5-year observations at the time of this analysis, a number too small for similar comparison. For all of the analyses that follow, patients from both enrollment periods were combined.

Table 9 presents the rates of progression to PDR at the 1-, 3-, and 5-year visits, with PDR divided into the early and high-risk categories. The proportion of eyes progressing increased with severity of baseline retinopathy level and length of follow-up, with the 5-year rate for level 53 reaching 57.8% for progression to the high-risk stage.

The possible prognostic importance of the severity of intraretinal characteristics in eyes that had early PDR at baseline is examined in Table 10, which classifies these eyes by the level to which they would have been assigned if proliferative lesions had been absent, and indicates the proportion of eyes in each group that progressed to high-risk PDR at the 1-, 3-, and 5-year follow-up visits. One-year rates of progression increased from 16.0% to 25.3% to 42.3% as the severity of intraretinal characteristics increased from level 43 to 47 to 53, respectively. Within each level, the rates for the various component definitions were generally similar to one another, except for IRMAs greater than or equal to M/1 in level 53, for which rates were relatively low at each follow-up period.

Table 11 presents the final scale, including levels less

Table 9. Percent of Eyes with Progression to Early and High-risk Proliferative Diabetic Retinopathy at the 1-, 3-, and 5-Year Visits, by Baseline Retinopathy Severity Level

Baseline Retinopathy Severity	1-Year Follow-up			3-Year Follow-up			5-Year Follow-up		
	Early (%)	High-risk (%)	No.*	Early (%)	High-risk (%)	No.*	Early (%)	High-risk (%)	No.*
Level 35	4.2	1.2	569	7.8	6.5	524	11.0	15.2	290
Level 43	8.3	3.6	839	15.6	13.3	758	21.0	24.5	457
Level 47	18.2	8.1	864	22.8	24.7	793	27.1	39.2	472
Level 53	33.1	17.1	522	26.9	44.4	468	21.6	57.8	301
Total	15.2	7.0	2794	18.3	21.2	2543	21.1	33.9	1520

* Number of eyes at risk.

Table 10. Percent of Eyes with Early Proliferative Diabetic Retinopathy at Baseline Progressing to High-risk Proliferative Diabetic Retinopathy at 1-, 3-, and 5-Year Visits, by Severity of Intraretinal Characteristics at Baseline

Severity of Intraretinal Characteristics at Baseline	1-Year Follow-up		3-Year Follow-up		5-Year Follow-up	
	Percent	No.*	Percent	No.*	Percent	No.*
Level 35						
C. RH present	50.0	2	50.0	2	50.0	2
D or E. HE ≥ D/1	0.0	4	50.0	4	66.7	3
F. SE ≥ D/1	25.0	12	40.0	10	40.0	5
Level 35 total	25.0	18	43.8	16	50.0	10
Level 43						
A. H/Ma = M/4–5, S/1	15.4	26	33.3	24	54.6	11
B. IRMA = D/1–3	16.3	49	37.8	45	58.3	36
Level 43 total	16.0	75	36.2	69	57.4	47
Level 47						
A. Both L43 definitions	20.3	59	45.3	53	43.8	32
B. IRMA = D/4–5	26.5	49	57.8	45	69.6	23
C. H/Ma = S/2–3	33.3	24	63.6	22	69.2	13
D. VB = D/1	26.1	46	57.1	42	74.2	31
Level 47 total	25.3	178	54.3	162	62.6	99
Level 53						
A. ≥2 L47 definitions	44.8	29	75.0	24	94.7	19
B. H/Ma ≥ S/4–5	38.1	21	76.2	21	76.9	13
C. IRMA ≥ M/1	22.4	67	53.1	64	62.2	45
D. VB ≥ D/2–3	49.2	122	70.4	108	82.2	73
E. ≥2 L53 definitions	47.9	94	74.4	86	75.4	57
Level 53 total	42.3	333	68.6	303	76.8	207
Total overall	33.4	604	59.7	550	69.7	363

RH = retinal hemorrhages; HE = hard exudates; SE = soft exudate; H/Ma = hemorrhages/microaneurysms; IRMA = intraretinal microvascular abnormalities; VB = venous beading.

* Number at risk.

and more severe than those considered in this report. The definition for each level assumes that the definition for any higher level is not met. The reproducibility of this scale was assessed by comparing independent duplicate gradings of the baseline photographs. Complete agreement on level was observed in 53% of eyes; agreement within 1 step was observed in 88% of eyes. The unweighted kappa statistic was 0.42 and weighted kappa was 0.65, with weight of 1 assigned to complete agreement, 0.75 to one-step disagreement, and 0 to all other disagreements.[4]

Table 12 presents the percentages of eyes with worsening of retinopathy by two or more levels between the

Table 11. ETDRS Final Retinopathy Severity Scale (for Individual Eyes)

Level	Severity	Definition
10	DR absent	Microaneurysms and other characteristics absent
14*	DR questionable	HE, SE, or IRMA definite; microaneurysms absent
15*	DR questionable	Hemorrhage(s) definite; microaneurysms absent
20	Microaneurysms only	Microaneurysms definite, other characteristics absent
35†	Mild NPDR	One or more of the following: Venous loops ≥ D/1; SE, IRMA, or VB = Q; Retinal hemorrhages present; HE ≥ D/1; SE ≥ D/1
43	Moderate NPDR	H/Ma = M/4–5 − S/1 *or* IRMA = D/1–3 (not both)
47	Moderately severe NPDR	Both L43 characteristics and/or one (only) of the following: IRMA = D4–5; H/Ma = S/2–3; VB = D/1
53	Severe NPDR†	One or more of the following: ≥2 of the 3 L47 characteristics; H/Ma ≥ S/4–5; IRMA ≥ M/1; VB ≥ D/2–3
61	Mild PDR	FPD or FPE present with NVD and NVE absent; or NVE = D
65	Moderate PDR	Either of the following: (1) NVE ≥M/1 or NVD = D; and VH and PRH = A or Q; (2) VH or PRH = D and NVE < M/1 and NVD absent
71	High-risk PDR	Any of the following: (1) VH or PRH ≥ M/1; (2) NVE ≥ M/1 and VH or PRH ≥ D/1; (3) NVD = 2 and VH or PRH ≥ D/1; (4) NVD ≥ M
75	High-risk PDR	NVD ≥ M and VH or PRH ≥ D/1
81	Advanced PDR: fundus partially obscured, center of macula attached	NVD = cannot grade, or NVD < D and NVE = cannot grade in ≥ 1 field and absent in all others; and retinal detachment at center of macula < D
85	Advanced PDR: posterior fundus obscured, or center of macula detached	VH = VS in fields 1 and 2; or retinal detachment at center of macula ⇒D
90	Cannot grade, even sufficiently for level 81 or 85	

DR = diabetic retinopathy, HE = hard exudates, SE = soft exudates, IRMA = intraretinal microvascular abnormalities, NPDR = nonproliferative DR, VB = venous beading, H/Ma = hemorrhages/microaneurysms, PDR = proliferative DR, NVE = new vessels elsewhere (>1 DD from disc), NVD = new vessels disc (within 1 DD of disc margin), FPD = fibrous proliferations disc, FPE = fibrous proliferations elsewhere, VH = vitreous hemorrhage, PRH = preretinal hemorrhage. For definitions of severity grades, see footnote of Table 2.

* Levels 14 and 15 are not considered separate steps in the scale, but are pooled with level 10 or 20.

† NPDR levels 35 and above all require presence of microaneurysms.

Table 12. Percent of Eyes with Retinopathy Progression of Two or More Levels at 1-, 3-, and 5-Year Visits, by Baseline Retinopathy Severity Level

Baseline Retinopathy Severity	1-Year Follow-up		3-Year Follow-up		5-Year Follow-up	
	Percent	No.*	Percent	No.*	Percent	No.*
Level 35	26.2	569	35.7	524	40.0	290
Level 43	22.0	840	37.5	758	50.3	457
Level 47	26.3	864	47.5	793	66.3	472
Level 53	32.4	522	58.1	468	68.1	301
Level 61	21.5	311	52.8	282	62.8	183

* Number at risk.

baseline and the 1-, 3-, and 5-year visits. One-year progression rates were quite similar across baseline levels, but 5-year rates increased somewhat with increasing level. The rates of improvement by two or more levels (not shown in the table) were small, ranging from 5 to 15%.

Because the baseline photographs were taken before the eye assigned to immediate treatment had received photocoagulation, retinopathy severity in this eye could also be assessed as a risk factor. Table 13 presents 1-, 3-, and 5-year rates of progression to PDR in eyes assigned to deferral, by baseline retinopathy severity level in this eye, subdivided by retinopathy level in the fellow eye. Retinopathy level in the fellow eye was related to pro-

Table 13. Percent of Deferral-Group Eyes with Progression to Proliferative Diabetic Retinopathy, at 1-, 3-, and 5-Year Visits, by Baseline Retinopathy Severity Level in Each Eye

Baseline Retinopathy Severity Level in Eye Assigned		1-Year Follow-up		3-Year Follow-up		5-Year Follow-up	
Deferral of Photocoagulation	Early Photocoagulation	Percent	No.*	Percent	No.*	Percent	No.*
35	<35	0.0	2	0.0	2		0
35	35	3.9	283	8.4	251	17.8	118
35	>35	7.0	284	20.2	253	37.4	123
43	<43	5.2	192	16.2	173	31.9	91
43	43	4.8	291	26.9	249	40.9	137
43	>43	21.4	356	36.5	307	54.3	164
47	<47	21.8	321	39.1	279	53.5	142
47	47	24.1	319	48.3	290	71.4	147
47	>47	35.7	224	57.8	206	73.4	128
55	<55	38.9	208	65.8	187	75.3	97
55	55	54.2	205	71.7	180	77.9	104
55	>55	64.2	109	81.9	94	91.2	57
Total		22.2	2794	39.5	2471	55.2	1308

* Number at risk.

gression rates, and on this expanded scale differences within deferral-group levels were generally greater than those between the highest subdivision of one such level and the lowest of the next.

Baseline duplicate gradings were used to assess the reproducibility of the "worse eye emphasized" method of classifying patients proposed by Klein and co-workers.[16] This method first assigns each patient to the level of his or her worse eye, then subdivides the patients within each level into two groups, those with the same retinopathy level in both eyes and those with a less severe level in the second eye. Patient retinopathy levels are expressed as level X/level X for patients with symmetrical levels and as level X/<level X for those with asymmetrical levels. The resultant patient retinopathy scale has twice as many steps as the eye scale, minus 1 (10/10, 20/<20, 20/20, 35/<35, 35/35. . .). There was complete agreement between two independent gradings in 38%, agreement within 1 step in 71%, and agreement within 2 steps in 87%. The unweighted kappa statistic was 0.31 and weighted kappa was 0.71, with weights of 1 for exact agreement, 0.9375 for one-step disagreement, 0.75 for two-step disagreement, and 0 for all other disagreements.

DISCUSSION

In the interim scale, eyes with hard exudates greater than or equal to M/1 had been moved down from level 4 of the scale of Klein and co-workers[16] into the mild NPDR group (level 30 of the interim scale; see Appendix table) because neither clinical impression nor DRS data suggested that the severity of hard exudates was prognostic for progression to PDR. In the final scale, eyes with soft exudates greater than or equal to D/1 also were lowered into the level 30 range because the risk of progression to PDR in eyes with soft exudates that did not have IRMAs, venous beading, or at least moderately extensive hemorrhages and/or microaneurysms was no greater than that in eyes with hard exudates that also were free of these characteristics. The remaining definitions included in level 35 were left unchanged from those of level 3 as proposed by Klein and co-workers.[16]

Because few eyes were included in the ETDRS that had very mild retinopathy, the definitions of the final scale regarding the lower range of NPDR could not be examined. For example, it could not be determined whether presence of mild retinal hemorrhages in addition to microaneurysms was sufficiently less severe than presence of hard or soft exudate to merit designation of separate levels for these two groups (i.e., division of level 35 into two parts).

For the range of retinopathy severity included in the ETDRS, the final scale provides convenient severity categories. Each category contains eyes with similar prognosis, and there is an orderly progression of risk with increasing category. It would be desirable if the proportions of eyes with progression of two or more levels were similar for all levels from mild to severe NPDR (Table 12), thus facilitating the use of worsening by two or more levels as a relatively sensitive measure of outcome over a broad range of baseline retinopathy severity. The scale comes close to this ideal for follow-up of 1 year, but not for longer periods.

When the scale is used for assessing change in overall retinopathy severity for patients, rather than eyes, classifying patients by retinopathy level in each eye (rather than by the worse eye, or by the right or left eye alone) retains prognostic information that would otherwise be lost (Table 13), and provides for a longer scale that has satisfactory reproducibility for change by three or more

Appendix Table. Percent of Eyes with Progression to Proliferative Diabetic Retinopathy at the 1-Year Visit, by Baseline Retinopathy Severity Level, Interim Scale

Baseline Retinopathy Severity Level and Component Definitions	Percent	No.*
Level 30		
A. Venous loops ≥ D	0.0	2
B. SE, IRMA, or VB = Q		0
C. RH present, H/Ma < S/1–3	4.4	23
D. HE = D	4.8	21
E. HE ≥ M/1	6.8	132
Level 30 total	6.2	178
Level 41		
A. IRMA = D/1–3	20.7	58
B. SE = D/1–3	10.2	481
Level 41 total	11.3	539
Level 45		
A. SE ≥ D/4–5	12.7	387
B. IRMA = D/4–5–M/1	32.2	118
C. VB = D/1	32.9	85
D. H/Ma = S/1–3	23.7	232
Level 45 total	20.7	822
Level 51		
A. H/Ma ≥ S/4–5	47.7	65
B. VB ≥ D/2–3	61.5	26
C. Combination of: SE ≥ D/2–3, IRMA ≥ D/2–3, and H/Ma ≥ S/1	39.3	140
Level 51 total	44.2	231
Level 55		
A. IRMA ≥ M/2–3	36.4	33
B. VB ≥ D/2–3 plus 2 other P2 characteristics	53.9	52
C. 4 P2 characteristics	65.0	40
D. H/Ma ≥ S/4–5 plus 2 other P2 characteristics	58.7	63
Level 55 total	54.8	188
Total overall	22.8	1958

SE = soft exudates; IRMA = intraretinal microvascular abnormalities; VB = venous beading; RH = retinal hemorrhages; H/Ma = hemorrhages/microaneurysms; HE = hard exudates. For definitions of severity grades, see footnote of Table 2.

* Number at risk.

steps, at least within the range of retinopathy severity included in the ETDRS.

APPENDIX

In the Appendix Table, which presents the 1-year rates of progression to PDR for the interim scale, a number of deficiencies are apparent. In level 41, 58 eyes with definite IRMAs in one to three fields (but free of SE), in which the 1-year progression rate was 20.7%, were grouped with (and below) 481 eyes with definite soft exudates in one to three fields, in which the 1-year rate was 10.2%. In level 45, 387 eyes with more severe SE, in which the 1-year rate was 12.7%, were included with other groups in which 1-year rates varied from 23.7 to 32.9%. Eyes placed in level 51B because venous beading was graded D/2-3 or greater (and because no definition of a higher level was met) had a progression rate like that of eyes in level 55. In defining levels 51 and 55, complex combinations of characteristics were used. Moreover, the two most severe levels were relatively small and 1-year progression rates did not differ greatly between them. These observations, together with the results shown in Tables 2 through 6, led to the revised definitions of the final scale.

An example is provided below to illustrate the process used in reaching the final scale (Table 7). The algorithm used for the next-to-last iteration placed eyes with hemorrhages and/or microaneurysms = M/4-5 in level 35, rather than level 43. There were 277 such eyes and their 1-year rate of progression to PDR was 9.0%. Most of these eyes (231) also had SE, and pooling them with other eyes with soft exudates in level 35 led to an increase in the progression rate for eyes with soft exudates to 6.5% (from 4.1% in the 243 eyes with soft exudates but with hemorrhages and/or microaneurysms less severe than M/4-5). The algorithm was changed (by redefining level 43A to include hemorrhages and/or microaneurysms = M/4-5) to move these eyes to level 43, because it seemed more appropriate to place them with eyes that had 1-year progression rates that were approximately 70% greater, namely 77 eyes with hemorrhages and/or microaneurysms = S/1 (1-year progression rate 15.6%) and 234 eyes with IRMAs = D/1-3 (1-year progression rate 15.0%) than with the eyes with soft exudates and less severe hemorrhages and/or microaneurysms, which they exceeded in progression rate by approximately double (4.1% versus 9.0%).

The final scale narrows the range of progression rates among the categories included within each level, divides eyes more evenly among levels, reduces the number of levels by one, and provides somewhat simpler definitions. The size of the mildest level is doubled and rates of progression in it are decreased slightly, with corresponding small increases in rates for eyes remaining in the 40s range. Level 53 in the final scale is almost as large as levels 51 and 55 of the interim scale combined and the rates of progression within level 53 are almost as great as those in level 55. Comparisons of the interim and final scales for 3- and 5-year progression rates yielded very similar results.

REFERENCES

1. Oakley N, Hill DW, Joplin GF, et al. Diabetic retinopathy I. The assessment of severity and progression by comparison with a set of standard fundus photographs. Diabetologia 1967; 3:402–05.
2. Lee P, McMeel JW, Schepens CL, Field RA. A new classification of diabetic retinopathy. Am J Ophthalmol 1966; 62:207–19.
3. Okun E, Cibis PA. The role of photocoagulation in the therapy of proliferative diabetic retinopathy. Arch Ophthalmol 1966; 75:337–52.
4. Early Treatment Diabetic Retinopathy Study Research Group. Grading diabetic retinopathy from stereoscopic color fundus photographs—an extension of the Modified Airlie House Classification:ETDRS report number 10. Ophthalmology 1991; 98:786–806.
5. Larsen H-W. Diabetic retinopathy: an ophthalmoscopic study with a discussion of the morphologic changes and the pathogenetic factors in this disease. Acta Ophthalmol [Suppl] 1960; 60:1–89.

6. Beetham WP. Visual prognosis of proliferating diabetic retinopathy. Br J Ophthalmol 1963; 47:611–19.
7. Dobree JH. Proliferative diabetic retinopathy: evolution of the retinal lesions. Br J Ophthalmol 1964; 48:637–49.
8. Davis MD. Natural course of diabetic retinopathy. In: Kimura SJ, Caygill WM, eds. Vascular Complications of Diabetes Mellitus: With Special Emphasis on Microangiopathy of the Eye. St. Louis: CV Mosby, 1967;139–69.
9. Davis MD, MacCormick AJA, Harris WAC, et al. Diabetic retinopathy prevalence and importance. In: Acta XXII Concilium Ophthalmologicum (Paris), 1974: Vol. 1;165–73.
10. Diabetic Retinopathy Study Research Group. Report 7. A modification of the Airlie House classification of diabetic retinopathy. Invest Ophthalmol Vis Sci 1981; 21:210–26.
11. The Diabetic Retinopathy Study Research Group. Photocoagulation treatment of proliferative diabetic retinopathy: the second report of Diabetic Retinopathy Study findings. Ophthalmology 1978; 85:82–106.
12. Rand LI, Prud'homme GJ, Ederer F, et al. Factors influencing the development of visual loss in advanced diabetic retinopathy. Diabetic Retinopathy Study (DRS) Report no. 10. Invest Ophthalmol Vis Sci 1985; 26:983–91.
13. The Diabetic Retinopathy Study Research Group. Indications for photocoagulation treatment of diabetic retinopathy: Diabetic Retinopathy Study Report no. 14. Int Ophthalmol Clin 1987; 27:239–53.
14. Deckert T, Simonsen SE, Poulsen JE. Prognosis of proliferative retinopathy in juvenile diabetes. Diabetes 1967; 16:728–33.
15. The Diabetic Retinopathy Study Research Group. Four risk factors for severe visual loss in diabetic retinopathy. The third report from the Diabetic Retinopathy Study. Arch Ophthalmol 1979; 97:654–55.
16. Klein BEK, Davis MD, Segal P, et al. Diabetic retinopathy. Assessment of severity and progression. Ophthalmology 1984; 91:10–17.
17. Davis MD, Hubbard LD, Trautman J, et al. Studies of retinopathy. Methodology for assessment and classification with fundus photographs. Diabetes 1985; 34(Suppl 3):42–9.
18. Early Treatment Diabetic Retinopathy Study Research Group. Design and baseline patient characteristics: ETDRS report number 7. Ophthalmology 1991; 98:741–56.
19. Early Treatment Diabetic Retinopathy Study Research Group. Photocoagulation for diabetic macular edema. Early Treatment Diabetic Retinopathy Study report number 1. Arch Ophthalmol 1985; 103:1796–806.
20. Efron B. Regression and ANOVA with zero-one data: measures of residual variation. J Am Stat Assoc 1978; 73:113–21.