EARLY PHOTOCOAGULATION IN PATIENTS WITH EITHER TYPE I OR TYPE II DIABETES

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ABSTRACT

Objective: To determine the benefits of early photocoagulation in patients with type I versus type II diabetes.

Design: One eye of each of 3,711 patients was randomly assigned to early photocoagulation; the other was assigned to deferral of photocoagulation, with follow-up visits scheduled every 4 months and photocoagulation to be carried out promptly if high-risk proliferative retinopathy developed. Patients were categorized by age and type of diabetes.

Main Outcome Measures: Best corrected visual acuity was measured at each study visit scheduled at 4-month intervals. Stereoscopic fundus photographs were taken and evaluated at baseline, 4 months, and yearly thereafter. Retinopathy severity was assessed from fundus photographs. Severe visual loss was defined as visual acuity of worse than 5/200 for at least two consecutive study visits.

Results: Previously published results of the Early Treatment Diabetic Retinopathy Study (ETDRS) demonstrated a statistically significant benefit of early photocoagulation in preventing severe vision loss. Further analyses demonstrate that this benefit of early photocoagulation is greater in patients with type II diabetes than in those with type I. The relative benefit of early photocoagulation in patients with type II diabetes is also seen for other outcomes (development of high-risk proliferative retinopathy, development of the combined end point [severe visual loss or vitrectomy], development of moderate visual loss, or development of legal blindness). The patients most likely to benefit from early photocoagulation had severe nonproliferative retinopathy or early proliferative retinopathy. Analyses from the Diabetic Retinopathy Study confirm the relative benefit of scatter photocoagulation for type II patients. Because of the high correlation between age and type of diabetes, analyses subgrouped by age show similar results.

Conclusion: These analyses suggest that patients with type II diabetes, or older patients with diabetes, are more likely to benefit from early scatter photocoagulation than patients with type I diabetes. The current standard of care is to initiate scatter photocoagulation as the severity of retinopathy approaches or reaches the high-risk stage. Provided careful follow-up is possible, ETDRS data do not show that initiating scatter photocoagulation prior to the development of high-risk proliferative diabetic retinopathy in patients with type I diabetes will reduce the risk of severe visual loss. ETDRS analyses do indicate that for patients with type II diabetes, it is especially important to consider scatter photocoagulation at the time of the development of severe nonproliferative or early proliferative retinopathy.

INTRODUCTION

Diabetic retinopathy has been and remains a leading cause of blindness in working-age adults.[1-4] However, for patients with severe nonproliferative diabetic retinopathy (SNPDR) or proliferative diabetic retinopathy (PDR), prompt intervention with scatter photocoagulation and vitrectomy when necessary can reduce the 5-year risk of severe visual loss by 90%.[5] A previous report of the Early Treatment Diabetic Retinopathy Study (ETDRS)[6] indicated that there is a small but statistically significant benefit of early photocoagulation in preventing severe visual loss, compared with deferring scatter until high-risk proliferative retinopathy develops. Although there are reports documenting that the natural history of type I diabetes is different from that of type II diabetes, no reports have demonstrated a difference in the efficacy of early scatter photocoagulation in these patients.[4,7-10]

Prior to the availability of treatment, the development of SNPDR or PDR was a reason for extreme concern by both patients and their physicians about the risk of impending blindness.[11-21] A 1963 study by Beetham[13] showed that about half of his patients who developed PDR became legally blind (visual acuity, ≤20/200 in the better eye) and that this occurred, on average, 3.2 years after the development of PDR. Other reports confirmed that within 5 years of onset of PDR, about 50% of patients were blind.[17,18]

During the 1960s and 1970s, numerous reports suggested that photocoagulation was an effective treatment for proliferative diabetic retinopathy, including six studies that incorporated concurrent control groups.[22-36] These early results were confirmed by the Diabetic Retinopathy Study, one of the first major randomized clinical trials in ophthalmology.[37-43] The control arm of that trial documented that untreated eyes with SNPDR or

PDR were at very high risk of blindness. After 3 years of follow-up, more than one third of these untreated eyes had reached the legal blindness level and nearly 30% had severe visual loss (visual acuity, <5/200).[37,43] Scatter photocoagulation reduced the risk of blindness by 60% in eyes treated in the Diabetic Retinopathy Study and became the standard of care for all eyes with high-risk PDR.[43-45] Subsequent clinical trials, the Diabetic Retinopathy Vitrectomy Study and the ETDRS, further demonstrated the marked effectiveness of prompt and thorough treatment for PDR.[46-52] In none of the reports from these large trials was there information indicating that older patients, or patients with type II diabetes, had a preferential benefit from photocoagulation. In fact, the Diabetic Retinopathy Vitrectomy Study reported that early vitrectomy for vitreous hemorrhage was somewhat more effective in type I diabetes or in younger patients with severe vitreous hemorrhage.[47,50]

One of the main questions addressed by the ETDRS was whether early scatter photocoagulation was preferable to deferring photocoagulation until high-risk PDR developed. As expected, early photocoagulation reduced the risk of developing high-risk PDR. However, the question of interest was whether it would lower the risk of blindness. As seen in Fig 1, all eyes in the ETDRS had low rates of severe visual loss, whether they received early photocoagulation or were in the deferral group (2.6% and 3.7%, respectively, at 5 years). The differences between early and deferral groups for severe visual loss reached borderline statistical significance (Mantel-Cox; P=0.035). The risks of either severe visual loss (SVL) or the

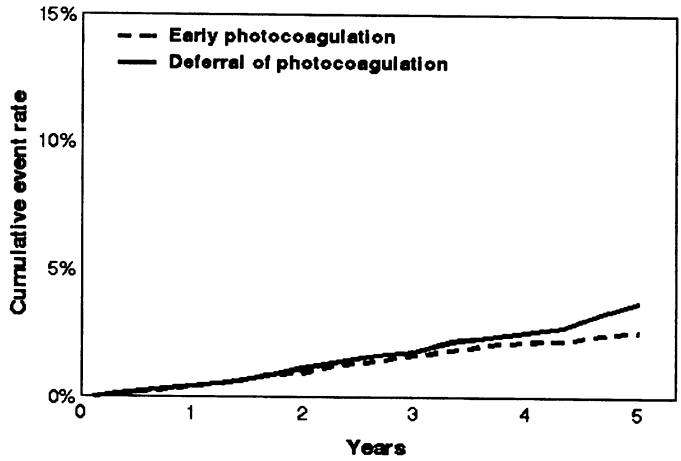

FIGURE 1
Development of severe visual loss in early treated eyes compared with deferred eyes p=0.035.

combined end point—SVL or vitrectomy (SVLV)—were higher for eyes with more severe retinopathy. Because the risks for this group were higher, and the chances that they would avoid scatter over a 5-year period were lower, the ETDRS research group concluded that as retinopathy approaches the high-risk stage (very severe nonproliferative retinopathy or moderate PDR), the benefits and risks of early photocoagulation may be roughly balanced and that early photocoagulation should be considered for such eyes. There was no analysis of the benefits and risks of early photocoagulation in subgroups divided by age or type of diabetes.

The Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) provides the best data to compare the relative risks of developing retinopathy in younger patients with diabetes, or patients with type I diabetes, and in older patients with diabetes, or patients with type II diabetes.[4, 7-10] Although there are other prevalence studies, WESDR has the largest population with the longest follow-up.[53-65] Because of the uncertainty of the type of diabetes or insulin dependency of individual patients in this population-based study, the investigators divided their population into those for whom the diagnosis of diabetes came before age 30 and those who were first diagnosed with diabetes at age 30 or older. The most important risk factor for the prevalence of retinopathy was duration of diabetes for either the younger-onset or older-onset patients. For patients who had had diabetes for less than 5 years, the prevalence of any retinopathy was highest in the older-onset patients. For patients who had had diabetes for more than 5 years, the prevalence of any retinopathy was highest in the younger-onset patients. Because the time of onset of diabetes is often difficult to know for older patients, it is reasonable to conclude that patients with younger-onset diabetes are at higher risk of developing any retinopathy than older-onset patients. After adjusting for the duration of retinopathy, the risk of having PDR was highest for patients with younger-onset diabetes, next highest for patients with older-onset diabetes who use insulin, and lowest for patients with older-onset diabetes who do not use insulin.

These differences in the prevalence of diabetic retinopathy for patients with younger-onset compared with older-onset diabetes are also seen for the incidence of diabetic retinopathy. WESDR data demonstrate that younger-onset patients have a higher incidence of "any retinopathy" at 4 and 10 years than do older-onset patients.[4, 9, 10] This is also true for the 4- and 10-year incidences of PDR.[4,9,10]

While there are population-based data to demonstrate that the risk of progression of retinopathy is higher in the younger-onset patients, there are no data evaluating the effect of scatter photocoagulation in younger-

onset versus older-onset patients. Many ophthalmologists presumed that because the risk of progression is highest in the younger patients, the need for earlier intervention with photocoagulation would be higher in this group. Data from the ETDRS can directly address this question.

MATERIALS AND METHODS

CLINICAL METHODS

The study design and methods of the ETDRS have been previously published.[51] A summary of these methods follows. The ETDRS enrolled 3,711 patients with diabetes mellitus whose eyes met the following criteria: (1) no macular edema, visual acuity of 20/40 or better, and moderate or severe nonproliferative or early proliferative diabetic retinopathy or (2) macular edema, visual acuity of 20/200 or better, and mild, moderate, or severe nonproliferative or early proliferative diabetic retinopathy. All patients were assigned randomly to receive 650 mg of aspirin per day or placebo. As previously reported, no effects of aspirin on retinopathy progression were found, and in this report, aspirin-treated and placebo-treated groups were pooled.[65]

One eye of each patient was assigned randomly to early photocoagulation and the other eye to deferral of photocoagulation, with follow-up visits scheduled every 4 months and photocoagulation to be performed promptly if high-risk proliferative diabetic retinopathy developed.

The type of early photocoagulation differed depending on the retinopathy at baseline. Three categories were defined on the basis of preliminary grading of fundus photographs and fluorescein angiograms. These differed in the presence or absence of macular edema and in retinopathy severity using the following definitions: *less severe* consisted of mild to moderate nonproliferative retinopathy, and *more severe* consisted of severe nonproliferative or early proliferative retinopathy. The strategies for early photocoagulation for each category are as follows:

- *Category 1: Eyes without macular edema.* Eyes in this category had moderate to severe nonproliferative or early proliferative retinopathy. Early photocoagulation for these eyes was either "full" or "mild" scatter.[51] Focal photocoagulation was to be initiated during follow-up if clinically significant macular edema (CSME) developed (ie, macular edema that involved or threatened the center of the macula).[66-68]
- *Category 2: Eyes with macular edema and less severe retinopathy.* Eyes in this category had macular edema and mild to moderate nonproliferative retinopathy. Early photocoagulation for these eyes consisted of

(1) immediate focal photocoagulation, with scatter photocoagulation (mild or full) added if severe nonproliferative or early proliferative retinopathy developed during follow-up, and (2) immediate scatter photocoagulation (mild or full), with focal photocoagulation delayed for at least 4 months. Eyes assigned to delayed focal photocoagulation received treatment at the 4-month visit if the edema had not improved clinically and the visual acuity score had not increased by five or more letters by that time. Focal photocoagulation was initiated at the 8-month visit if the edema was not substantially improved, as demonstrated by either a return of an initially thickened macular center to normal thickness or improvement in visual acuity score by 10 or more letters. At and after the 12-month visit, initiation of focal photocoagulation was required for all eyes assigned to early photocoagulation if they had CSME and had not yet received focal photocoagulation.

- *Category 3: Eyes with macular edema and more severe retinopathy.* Eyes in this category had macular edema and severe nonproliferative or early proliferative diabetic retinopathy. Early photocoagulation for these eyes consisted of (1) immediate focal and scatter photocoagulation (mild or full) or (2) immediate scatter photocoagulation (mild or full), with focal photocoagulation delayed for at least 4 months. The same procedure described in category 2 for initiating focal photocoagulation at or after 4 months was used.

Although there are four different strategies for the timing and extent of early photocoagulation, they are randomized and therefore equally distributed in both diabetes I and diabetes II groups. Also, after 1 year of follow-up, the eventual amount of treatment in the early group is similar for all patients. They all received scatter originally, and if the retinopathy progressed to high-risk PDR, the mild scatter group has received full scatter. If they had macular edema or developed it, they have received focal treatment. There are no statistically significant interactions on the outcome variables SVL or SVLV of these early treatment strategies (mild versus full scatter or immediate versus delayed focal treatment for macular edema) and type of diabetes. All early treatment strategies are therefore combined in these analyses.

METHODS FOR ASSESSING TYPE OF DIABETES

In 1979, the National Diabetes Data Group (NDDG) recommended a classification system for patients with diabetes.[69] In the NDDG classification, persons who were insulin-dependent and ketosis-prone were labeled as having type I diabetes, or insulin-dependent diabetes mellitus (IDDM). Those who were non-insulin-dependent and non-ketosis-prone were

labeled as having type II diabetes, or non-insulin-dependent diabetes mellitus (NIDDM). Fasting and stress C-peptide levels were assessed in a subgroup of ETDRS patients in an attempt to develop an algorithm that could be used to classify all patients enrolled in the study. Using historical information collected for each patient (age at onset of diabetes, insulin use, and percent desirable weight), patients were classified into two groups—"broad type I" and "broad type II"—or into three groups—type I, intermediate, or type II. In the analyses in this report, the broad definition, which classifies patients into one of two groups, was used. Broad type I is defined as age of 30 years or less at time of diabetes diagnosis and continuous insulin use started within 1 year of diagnosis, *or* age of 40 years or less at time of diabetes diagnosis, continuous insulin use started within 1 year of diagnosis, and desirable weight less than 120%. Patients not meeting these criteria were classified as broad type II.

The accuracy of the classification could be tested using the ETDRS subgroup for which the C-peptide status was known. The predictive value of the broad classification system developed from these data for use in the ETDRS was 93.4% for type I (IDDM) and 82.8% for type II (NIDDM).[70] Overall, there was a 93.6% agreement between the broad classification system and the classification of diabetes by discriminant analysis (using post-Sustacal C-peptide levels and data available from the ETDRS medical form). On the basis of this information, type of diabetes is likely to be classified correctly for most ETDRS patients.

METHODS FOR ASSESSING OUTCOME VARIABLES

Best-corrected visual acuity was measured with logarithmic visual acuity charts at baseline and each subsequent follow-up visit, scheduled at 4-month intervals.[71] A standardized protocol for the collection of visual acuity measurements was used in all clinical centers. The protocol specified that visual acuity examiners be trained and certified and that they be masked from treatment assignment.[51]

Stereoscopic 30° color photographs were taken of seven standard fields at baseline, 4 months, 1 year after entry, and yearly thereafter. All fundus photographs were graded according to a standardized procedure by the Fundus Photograph Reading Center staff, who had no knowledge of treatment assignments and clinical data.[72-74]

STATISTICAL METHODS

Multivariable survival analyses and Cox proportional hazards models were performed to assess the effect of early treatment on the following outcomes: time to development of high-risk proliferative retinopathy, SVL,

and SVL or vitrectomy.[75-76] All Cox proportional hazards models were adjusted for age, duration of diabetes, and retinopathy severity. Additional analyses were performed assessing the proportion of patients during follow-up with a doubling of their initial visual angle, or visual acuity of less than 20/100. A two-sample z-test of equality of proportions was used when comparing proportions of eyes with a given outcome.[77] Values corresponding to a P value of < 0.01 were considered statistically significant for main effects and interactions. Multivariate Cox regression models were also fit to adjust for the correlated nature of the observations between eyes within a patient across the period of follow-up.[78,79]

RESULTS

As part of a series of analyses assessing possible risk factors for blindness in ETDRS patients, we observed that when patients were classified by diabetes type, the difference in treatment benefit, comparing early photocoagulation with deferral, was greatest in the type II patients (Fig 2).[9] This increased benefit of early photocoagulation in type II patients was statistically significant (Cox regression for SVL: interaction of early photocoagulation and type of diabetes, P=0.0003).

Analyses that categorized patients by age showed similar, but less statistically significant, interactions of treatment effect and age, both when age was used as a continuous variable and when patients were categorized

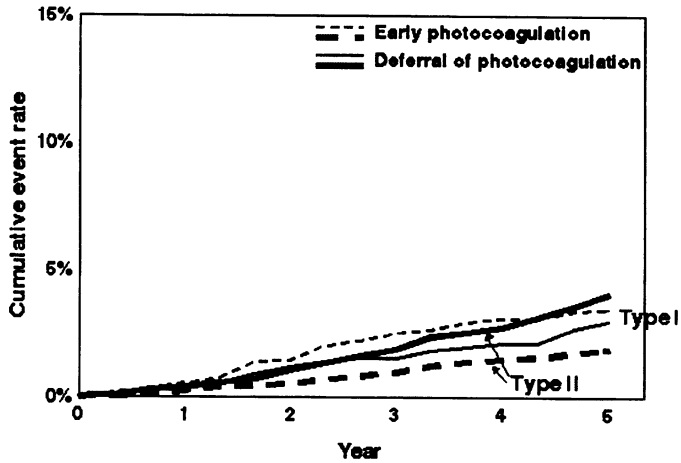

FIGURE 2

Development of severe visual loss in early treated eyes compared with deferred eyes, for patients with type I (p=0.23) and type II (p=0.0002) diabetes. Test for interaction of treatment and type, p=0.0003.

into two age-groups (≤ 40 and > 40 years). Categorizing age into these two groups results in an 88% overlap with the categorization of patients by type of diabetes (Table I). Therefore, it is not surprising that the results of analyses for interaction with treatment effect are similar whether age or type of diabetes is used to classify patients. There is inadequate power to determine if there is an age effect within type of diabetes, so we are unable to distinguish between the effect of these two variables. However, interactions with treatment effect using type of diabetes subgroups were somewhat more statistically significant than the interactions with age subgroups (Cox regression for SVL: interaction of treatment and type of diabetes, P=0.001; interaction of treatment and age [continuous variable], P=0.001; interaction of treatment and age [dichotomized as ≤age 40 and >age 40], P=0.01).

TABLE I. CATEGORIZATION OF PATIENTS BY AGE AND DIABETES TYPE

	TYPE OF DIABETES		
	I	II	TOTAL
Age ≤40	1,116	127	
Age >40	328	2,140	
Total			3,711

Models that included both type of diabetes and age also showed the interaction of treatment effect with type of diabetes to be more statistically significant than the age interaction (Cox regression for SVL: interaction of treatment and type of diabetes, P=0.04; interaction of treatment and age [dichotomized], P=0.91). Because the interaction was more statistically significant with type of diabetes than with age, all further analyses presented will be subgrouped by type of diabetes. However, no important differences were found qualitatively when comparing the analyses, subgrouped by diabetes type, with those subgrouped by age, and it is reasonable to assume that conclusions based on type of diabetes interactions are true, but to a somewhat lesser extent for age. As a clinical variable, age ≥40 may be somewhat easier to use than type of diabetes. All analyses subgrouped by type of diabetes were repeated, but subgrouped by age, and can be found in the appendix identified by the appropriate table or figure

number. Table II provides the denominators for analyses based on all eyes and on the subgroup of eyes with more severe retinopathy.

TABLE II. ETDRS PATIENT POPULATION

	NO. OF EYES, BY TYPE OF DIABETES		
TREATMENT	**I**	**II**	**TOTAL**
Early photocoagulaton	1,444	2,267	
Deferral of photocoagulation	1,444	2,267	
Total	2,888	4,534	7,422
	NO. OF EYES WITH SNPDR OR EPR, BY TYPE OF DIABETES		
TREATMENT	**I**	**II**	**TOTAL**
Early photocoagulaton	680	557	
Deferral of photocoagulation	674	584	
Total	1,354	1,141	2,495

SNPDR, severe nonproliferative diabetic retinopathy; EPR, early proliferative retinopathy.

As shown in Fig 3, early photocoagulation was also more effective in type II patients for the combined outcome variable, severe visual loss or vitrectomy (Cox regression for SVLV: interaction of treatment and type of diabetes, P=0.0001). This combined outcome variable provides more events and increases the power to assess differences in subgroups but has the drawback of possible bias. Some study ophthalmologists may have been more likely to do a vitrectomy earlier in younger patients on the basis of on results from the Diabetic Retinopathy Vitrectomy Study.[47, 50] All analyses were done for both outcome variables (SVL and SVLV), and there were no qualitative differences between analyses using SVL alone versus the combined end point SVLV. Thus, there was no evidence of an effect of this potential bias on the interaction of early treatment with diabetes type when comparing SVL analyses with SVLV analyses.

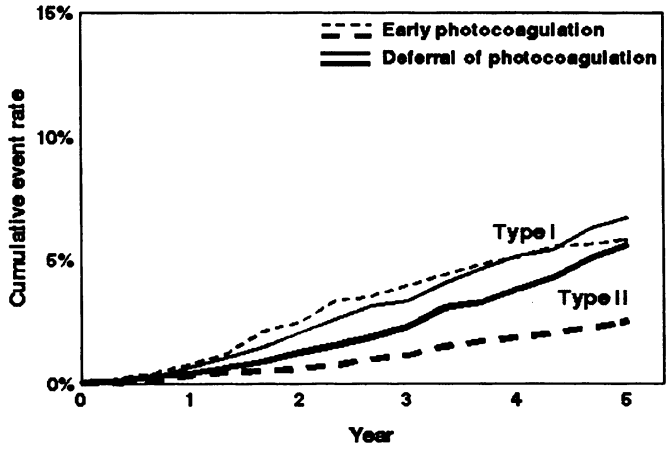

FIGURE 3

Development of severe visual loss or vitrectomy in early treated eyes compared with deferred eyes, for patients with type I (p=0.47) and type II (p=0.0001) diabetes. Test for interaction of treatment and type, p=0.0001.

If there is a benefit of early photocoagulation in type II patients, when should treatment be initiated? Fig 4A shows the rates to SVLV for patients with mild to moderate nonproliferative retinopathy at baseline. In this group of patients with milder retinopathy, the rates to SVLV were low for

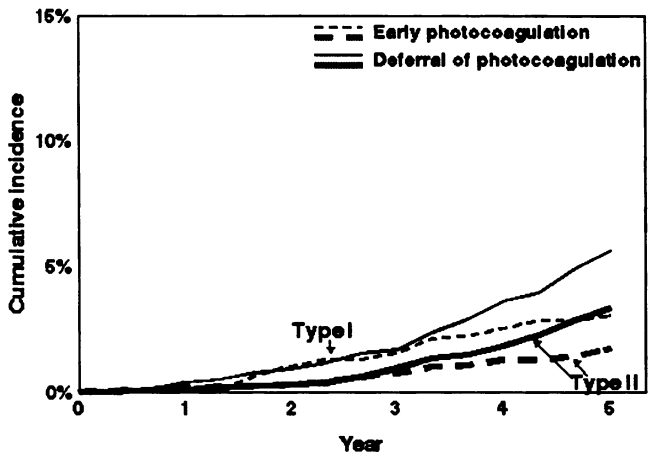

FIGURE 4A

Development of severe visual loss or vitrectomy in eyes with mild to moderate nonproliferative retinopathy at baseline. Early treated eyes compared with deferred eyes, for patients with type I (p=0.03) and type II (p=0.01) diabetes. Test for interaction of treatment and type, p=0.87.

both types of diabetes and for both treatment groups, although in general, patients with type I diabetes had higher rates. No benefit of early treatment was seen for the first 3 years, and thereafter the benefits were similar in the two diabetes groups, but of borderline statistical significance.

For patients with more severe retinopathy (Fig 4B), the risk of SVLV was higher than in the less severe retinopathy group for both types of diabetes and both treatments. When the retinopathy is this severe and treatment is deferred, type II patients have rates of SVLV that are equal to, or even higher than, type I patients. Type II patients had a 50% reduction in the rate to SVLV if they received early treatment (Mantel-Cox; P=0.0001), whereas early photocoagulation in type I patients was somewhat worse than deferring photocoagulation until high-risk PDR, but the difference was not statistically significant (Mantel-Cox; P=0.43). The interaction of treatment effect and type of diabetes was statistically significant (Cox; P=0.0002).

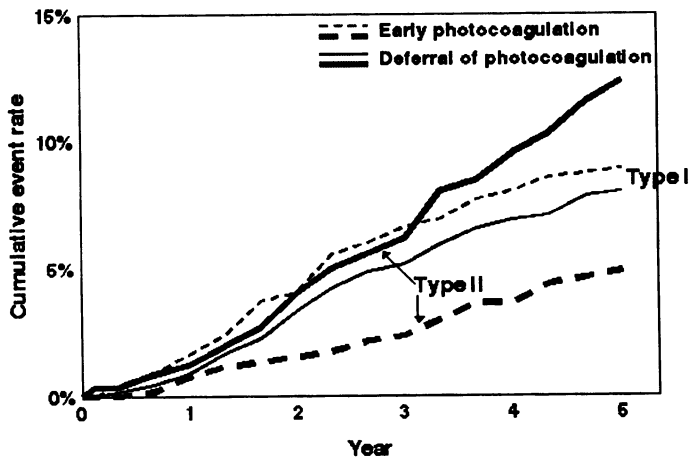

FIGURE 4B

Development of severe visual loss or vitrectomy in eyes with severe non-proliferative or early proliferative retinopathy at baseline. Early treated eyes compared with deferred eyes, for with type I (p=0.43) and type II (p=0.0001) diabetes. Test for interaction of treatment and type, p=0.0002.

Because most eyes developing SVLV first developed high-risk characteristics, we analyzed the risk of progression to high-risk proliferative diabetic retinopathy (HRPDR), which was a much more frequent event than SVLV, as an alternative outcome. Among eyes assigned to deferral, the rate of progression to HRPDR was consistently higher in the deferred eyes of

type I patients than in those of type II patients (Fig 5). Early photocoagulation reduced these rates in both of the diabetes subgroups. The reduction was about 50% in type II and about 30% to 40% in type I (Cox regression for HRPDR: interaction of treatment and type of diabetes, P=0.008).

However, when we subdivide by severity of retinopathy, we see a different picture, especially in the more severe retinopathy subgroup (Fig 6). In eyes with less severe retinopathy, the type II patients have a lower risk of progression to HRPDR than the type I patients, and both groups of eyes receiving early photocoagulation had a comparable reduction in the rate to HRPDR compared with the deferral groups (Fig 6A).

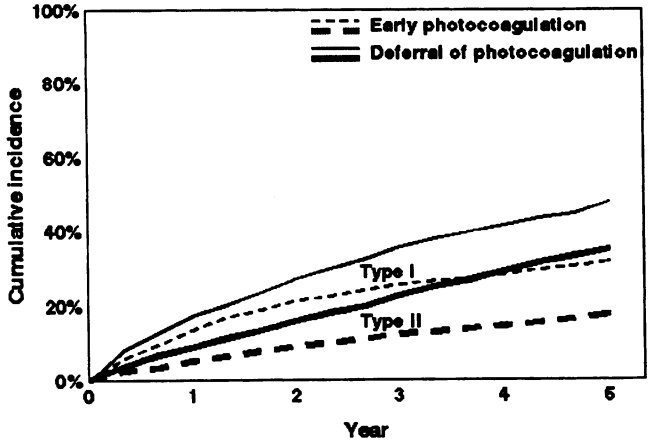

FIGURE 5

Development of high-risk proliferative diabetic retinopathy in early treated eyes compared with deferred eyes, for patients with type I (p=0.0001) and type II (p=0.0001) diabetes. Test for interaction of treatment and type, p=0.008.

For eyes with more severe retinopathy assigned to deferral, the rate to HRPDR was the same for both types of diabetes (Fig 6B). Eyes of type I patients assigned to early treatment had some reduction in this rate, while eyes of type II patients receiving early photocoagulation had a considerably larger reduction in the rate to HRPDR. This interaction of early photocoagulation and diabetes type in the eyes with more severe diabetic retinopathy was statistically significant (Cox regression for HRPDR: interaction of treatment and type of diabetes, P=0.002).

Data from the Diabetic Retinopathy Study provide further evidence of an increased benefit of scatter photocoagulation in type II patients. Figure 7 shows the risk of development of SVL in Diabetic Retinopathy

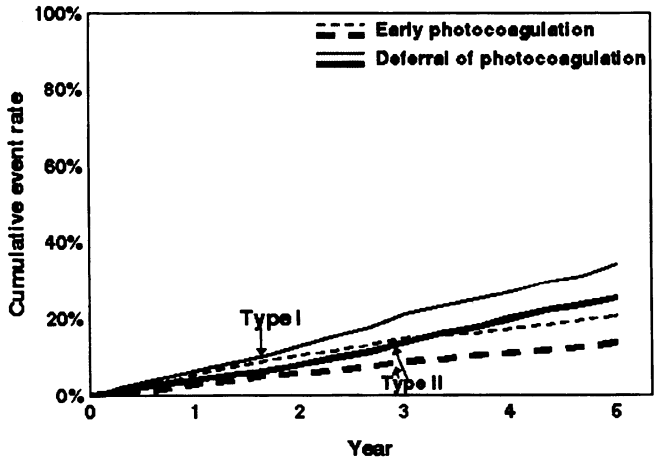

FIGURE 6A

Development of high-risk proliferative diabetic retinopathy in eyes with mild to moderate nonproliferative retinopathy at baseline. Early treated eyes compared with deferred eyes, for patients with type I (p=0.0001) and type II (p=0.0001) diabetes. Test for interaction of treatment and type, p=0.32.

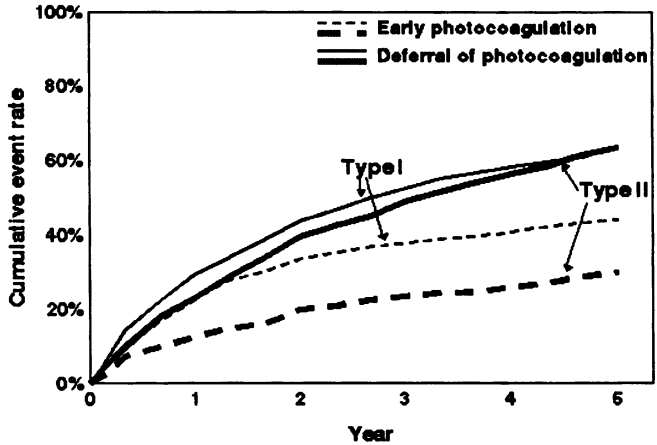

FIGURE 6B

Development of high-risk proliferative diabetic retinopathy in eyes with severe nonproliferative or early proliferative retinopathy at baseline. Early treated eyes compared with deferred eyes, for patients with type I (p=0.0001) and type II (p=0.0001) diabetes. Test for interaction of treatment and type, p=0.002.

Study eyes subgrouped by type of diabetes. The benefit of photocoagulation was larger in patients with type II diabetes (Cox regression: treatment and type of diabetes interaction, P = 0.001).

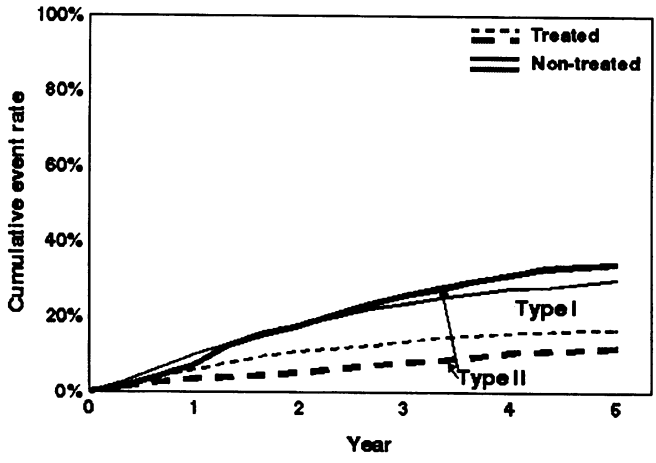

FIGURE 7
Development of severe visual loss in the Diabetic Retinopathy Study. Treated eyes compared with nontreated eyes, for patients with type I (p=0.0001) and type II (p=0.0001) diabetes. Test for interaction of treatment and type, p=0.001.

Scatter photocoagulation seems to have a larger treatment effect in type II patients with severe diabetic retinopathy than in type I patients with similar retinopathy. Before recommending early scatter photocoagulation for type II patients, we must assess possible side effects. Scatter photocoagulation reduces peripheral visual field, and this should be considered when balancing risk and benefits of early treatment.[6] There is little to suggest that this side effect of scatter photocoagulation would be clinically different in type I versus type II patients. However, previous reports show that type II patients with diabetes are more likely to have macular edema, and that scatter photocoagulation in eyes with macular edema can result in some loss in visual acuity.[6]

Two additional visual acuity outcome variables were evaluated: the proportion of patients with a doubling of their baseline visual angle (moderate visual loss) and the proportion of patients with visual acuity of worse than 20/100 (equivalent to legal blindness). Because any early treatment recommendations would be limited to the more severe retinopathy subgroups, these analyses are limited to these groups (in the ETDRS these groups all received scatter as part of their initial early treatment). The proportion of eyes with moderate visual loss during follow-up is shown in Fig 8. Patients with type II diabetes were more likely to have moderate visual acuity loss during follow-up than patients with type I diabetes. However, there is no evidence that early scatter (which included focal treatment for

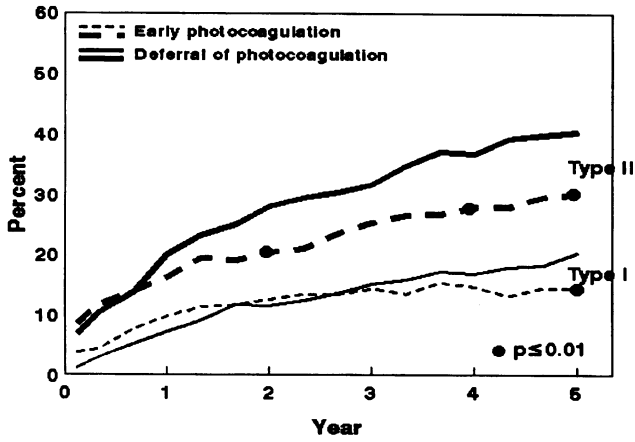

FIGURE 8

Proportion of eyes with decrease in visual acuity (doubling of visual angle) compared to baseline in early treated eyes compared with deferred eyes, for patients with type I and II diabetes. In patients with type I diabetes, a significant treatment effect was observed at 5 years (p=0.01). In patients with type II diabetes, significant treatment effects were observed at 2, 4, and 5 years (p<0.01).

macular edema when present) was more likely to cause a doubling of the initial visual angle than deferring treatment (with the possible exception of a trend toward slightly more visual acuity loss in the first year after treatment).[6] Any apparent benefit of early photocoagulation may be in part because eyes assigned to deferral did not receive any focal photocoagulation for macular edema until the ETDRS results demonstrating that focal treatment was effective were released (average follow-up at that time about 2 years: 35% of patients with 3 years of follow-up and 20% with less than 1 year of follow-up).[66]

Figure 9 shows the effect of early photocoagulation in eyes with more severe retinopathy, with and without CSME. For eyes with more severe retinopathy and CSME (Fig 9A), the risk of moderate visual acuity loss (a doubling of their initial visual angle) is higher in type II patients than in type I patients. However, for type II patients, the risk of moderate visual acuity loss is lower in the early photocoagulation group, despite the early scatter treatment. There is little, if any, difference between early photocoagulation and deferral of photocoagulation for type I patients. As previously noted, there is some increased loss of visual acuity during the first year of follow-up in eyes with preexisting macular edema that received early photocoagulation, and any benefit of early photocoagulation might be less if the deferred eyes had received immediate focal photocoagulation

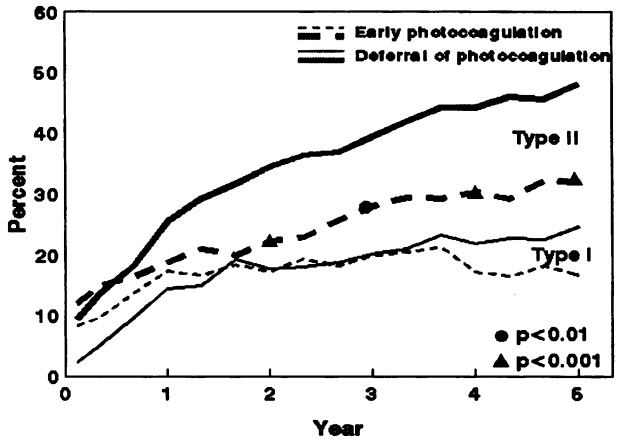

FIGURE 9A

Proportion of eyes with decrease in visual acuity (doubling of visual angle) compared to baseline in eyes with severe nonproliferative or early proliferative retinopathy baseline, early treated eyes compared with deferred eyes, for patients with clinically significant macular edema at baseline. In patients with type II diabetes, significant treatment effects were observed at 2, 4, and 5 years ($p<0.001$) and at 3 years ($p<0.01$).

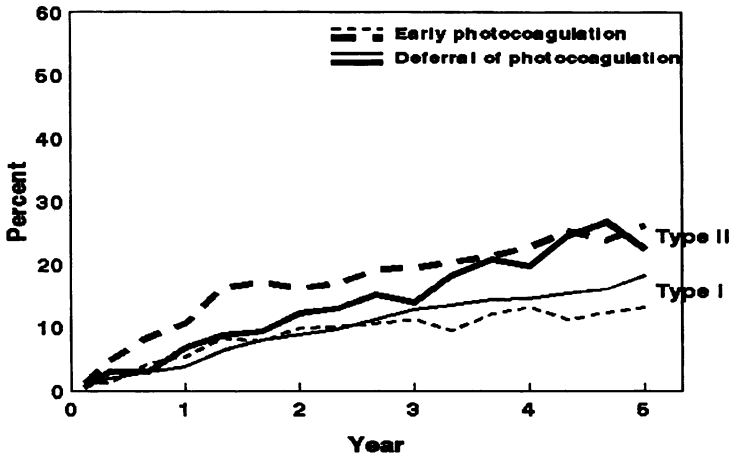

FIGURE 9B

Proportion of eyes with decrease in visual acuity (doubling of visual angle) compared to baseline in eyes with severe nonproliferative or early proliferative retinopathy baseline, early treated eyes compared with deferred eyes, for patients without clinically significant macular edema at baseline, for patients with type I and II diabetes.

for macular edema. There is nothing to indicate that early treatment in patients with type II diabetes and CSME caused harm.

For eyes without CSME (Fig 9B), there were trends for some decrease in visual acuity in the early photocoagulation group for the first several years, especially for type II patients, but there were no statistically significant differences.

Rates to legal blindness, for eyes with more severe retinopathy at baseline, are shown in Fig 10. Type II patients were more likely to reach this outcome than type I patients, but these patients were also more likely to benefit from early photocoagulation.

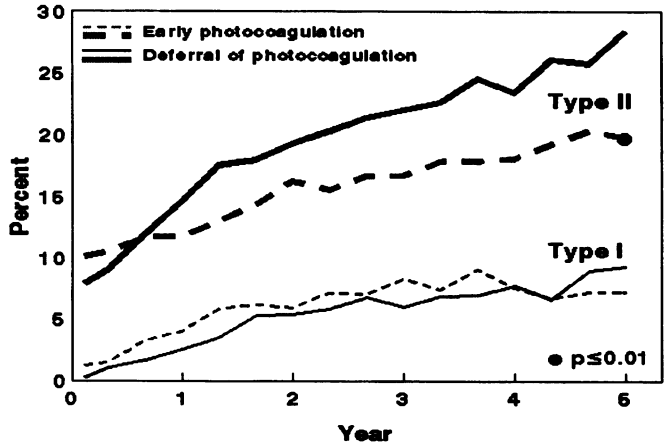

FIGURE 10

Proportion of eyes with visual acuity worse than 20/100 during follow-up in eyes with severe nonproliferative or early proliferative retinopathy at baseline, early treated eyes compared with deferred eyes, for patients with type I and II diabetes. In patients with type II diabetes, significant treatment effect was observed at 5 years (p=0.01).

DISCUSSION

The finding that the effect of scatter photocoagulation in reducing SVL is greater in patients with type II diabetes than in those with type I diabetes was not anticipated during the design phase of the ETDRS. Subgroup analyses, including those using type of diabetes, were planned. However, they were never thought of as primary analyses, and this finding of an interaction of an early photocoagulation treatment effect with type of diabetes, or age, must be carefully evaluated before it can be accepted.

As with all study results, we must assess whether the result could reasonably be attributed to chance, confounding, or bias. Confounding and bias are unlikely causes for this finding because of the randomized nature of the treatment groups and the masked assessment of outcome variables

(with the exception of vitrectomy as an end point, as previously discussed).

It is more difficult to rule out that this apparent interaction may be due to chance. Many possible interactions were reviewed as part of ETDRS analyses. The nominal *P* value does not take into account these "multiple looks." For example, if we reviewed 100 different interactions, it is quite likely that we would find one that would reach the nominal level of $P<0.01$. To make this point, we divided the ETDRS population by daily birth date. We define those born on days 6, 8, 9, 10, 12, 14, 18, 20, 21, 24, 26, and 29 as "group l" and those born on any other day as "group 2." As seen in Fig 11 there is an interaction with this birth date variable and treatment effect that is very similar to that seen with type of diabetes and is about as statistically significant (Mantel-Cox; $P<0.00l$).

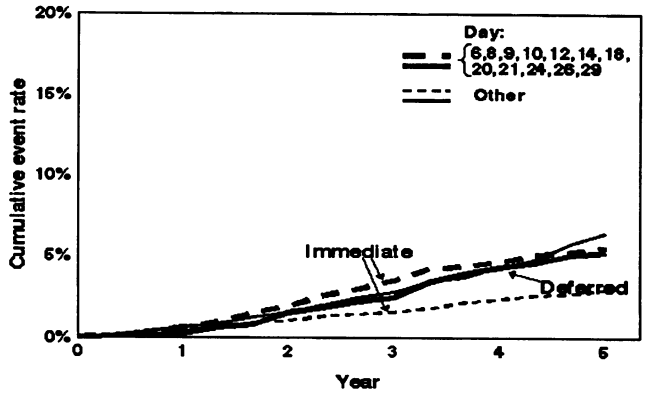

FIGURE 11

Development of severe visual loss in early treated eyes compared with deferred eyes, for patients in birth date group 1 compared with birth date group 2. Test for interaction of treatment and birth date group, $p<0.001$.

Just because it is almost impossible to rule out chance as the reason for the interaction does not mean that the interaction is not true. To gain assurance that the finding is real, we can look for consistency of results. If we can independently verify the finding, then chance is an unlikely cause. The first attempt to verify the interaction is to assess the magnitude of the interaction for outcome variables other than SVL. The interaction with treatment effect was also present for the variable SVLV. This is important because vitrectomy can be considered a bad outcome, but it helps little in ruling out chance, since this variable and SVL are highly correlated. Similarly, the results in eyes with more severe retinopathy, demonstrating that scatter photocoagulation is more effective in slowing the progression

to high-risk PDR in type II patients than type I patients, may help us understand the mechanism of the interaction but helps little in ruling out chance.

Data from the DRS are independent from ETDRS data. The fact that there was also a statistically significant interaction of early photocoagulation treatment effect and type of diabetes in that study does reduce the likelihood that the interaction found in the ETDRS is due to chance.

If older or type II patients are truly more likely to benefit from early scatter photocoagulation, when should it be initiated? It is apparent from the analyses that the benefit of early scatter in type II or older patients is limited to eyes with more severe retinopathy (SNPDR and PDR). For these patients, early scatter reduces the risk of developing high-risk PDR, SVL, and the combined outcome SVLV. However, particularly for eyes with macular edema, is there a risk of moderate visual loss associated with early scatter photocoagulation? Although eyes treated with early photocoagulation were somewhat more likely to have visual acuity loss in the first year following treatment, the older or type II patients were statistically significantly better off for all visual outcomes studied (with the exception of moderate visual acuity loss in eyes without CSME, where there was no statistical difference between early and deferral groups). This suggests that scatter photocoagulation when the retinopathy severity reaches the severe nonproliferative or early proliferative stage may be particularly beneficial for these older or type II patients. Conversely, ETDRS data do not provide any evidence that initiating scatter photocoagulation prior to the development of high-risk proliferative diabetic retinopathy in patients with type I diabetes will reduce the risk of SVL, SVLV, or moderate visual acuity loss, provided the patients can be carefully followed and treated when high risk develops.

What possible mechanism could explain the finding that scatter treatment is more effective in the older or type II patients? The simplest hypothesis might be related to the amount of stimulus for neovascularization. One could hypothesize that even for apparently identical amounts of retinopathy, the younger patients have more angiogenic factor (such as vascular endothelial growth factor) being released than the older patients.[80-83] Photocoagulation in older patients might be more effective because there is less of an angiogenic effect to begin with. This explanation is made less attractive by the fact that the interaction is most apparent in the eyes with more severe retinopathy (SNPDR and early PDR). In this group of eyes, the rates of development of HRPDR and SVL (or SVLV) are very similar for both the type I and type II groups assigned to deferral. This might suggest that either the neovascular stimulus is equal

in both groups or, if the amount of angiogenic factor is less in the older group, they are more sensitive to it.

A second possibility is that there is a subgroup of type I patients that are particularly subject to an adverse effect of early scatter photocoagulation, or that there is a subgroup of type II patients with more severe retinopathy that are particularly benefited by early scatter photocoagulation. Analyses thus far have not identified any such subgroups.

A third possibility is that there are several factors involved. There are reports linking capillary nonperfusion with the progression of diabetic retinopathy to the proliferative stage.[84-86] It may be that older persons or persons with type II diabetes decompensate at a faster rate when the vascular bed is stressed with the changes of diabetic retinopathy. Because older blood vessels cannot compensate as well to changes in blood flow, they may be more likely to close, leading to capillary nonperfusion.[87-89] This may be one of the reasons that the risk of vascular occlusions is age-related.[90-93]

Scatter photocoagulation may return retinal blood flow and autoregulation toward normal values, with dilated retinal veins returning to near-normal diameters.[94-99] This change may be more important to an older eye than to a younger eye. The progression of diabetic retinopathy may be faster in the younger group, but their ability to compensate for hemodynamic change may explain why early photocoagulation is less effective in this group. For this group, the disease progression and the increased amounts of angiogenic stimulus created by it may be the main factor in the final outcome. The timing of scatter photocoagulation may be less important.

For the older, or type II patients, the rate of progression of the retinopathy may be slower, but when they reach the severe nonproliferative stage, they may be more likely to decompensate with widespread nonperfusion. The effect of early scatter photocoagulation in reverting the hemodynamics toward normal may reduce this component of risk for capillary nonperfusion. This would then leave the diabetic retinopathy and associated angiogenic stimulus, which may be less for the older patient, as the main cause of progression to PDR. This stimulus would also be directly reduced by scatter photocoagulation. The effect of early scatter on two risk factors for neovascularization (angiogenic factor production and vascular decompensation), one of which is more important in the older patients, could explain the observation of a treatment interaction.

Uncertainty as to why a treatment is effective is not a reason to avoid using it. We still do not know for certain why photocoagulation is an effective treatment for diabetic retinopathy, but there can be no doubt that it is

effective in reducing the risk of blindness.[5,6,37-45] These analyses suggest that early scatter photocoagulation is particularly effective in older or type II patients.

The current standard of care is to initiate scatter photocoagulation as the severity of retinopathy approaches or reaches the high-risk stage. These results indicate that initiating scatter photocoagulation prior to the development of high-risk proliferative diabetic retinopathy in patients with type I diabetes will not reduce the risk of severe visual loss, provided careful follow-up is possible. The results also indicate that for older, or type II, patients, it is especially important to consider scatter photocoagulation at the time of the development of severe nonproliferative or early proliferative retinopathy.

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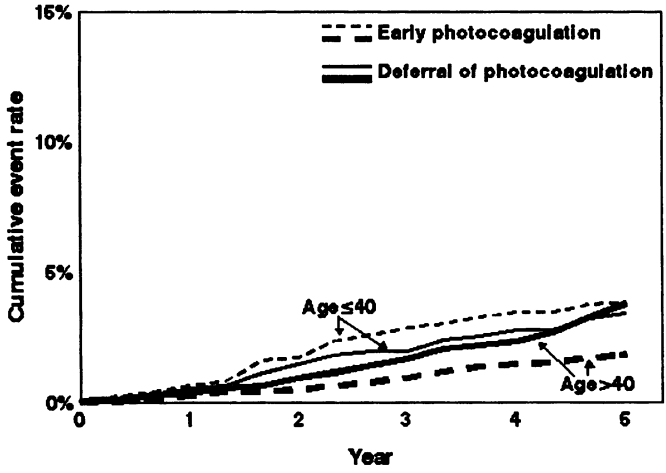
APPENDIX

APPENDIX TABLE II. INTERACTION OF TREATMENT EFFECT WITH AGE

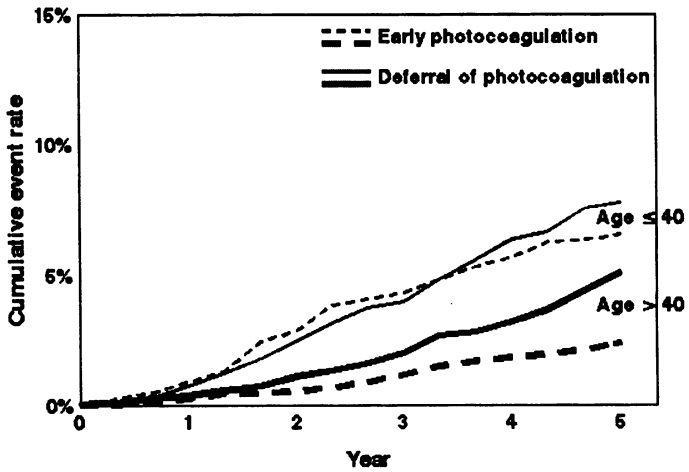
	NO. OF EYES, BY AGE		
TREATMENT	**AGE ≤ 40**	**AGE > 40**	**TOTAL**
Early photocoagulaton	1,243	2,468	
Deferral of photocoagulation	1,243	2,468	
Total	2,486	4,936	7,422
	NO. OF EYES WITH SNPDR OR EPR, BY AGE		
TREATMENT	**AGE ≤ 40**	**AGE > 40**	**TOTAL**
Early photocoagulaton	642	595	
Deferral of photocoagulation	640	618	
Total	1,282	1,213	2,495

EPR, early proliferative retinopathy; SNPDR, severe nonproliferative diabetic retinopathy.



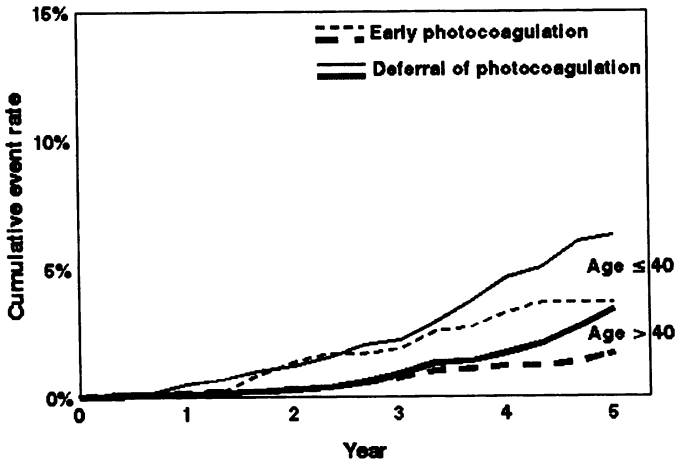
APPENDIX FIGURE 2

Development of severe visual loss in early treated eyes compared with deferred eyes, for patients ≤ 40 years of age (p=0.47) and for patients > 40 years (p=0.001). Test for interaction of treatment and age, p=0.01.



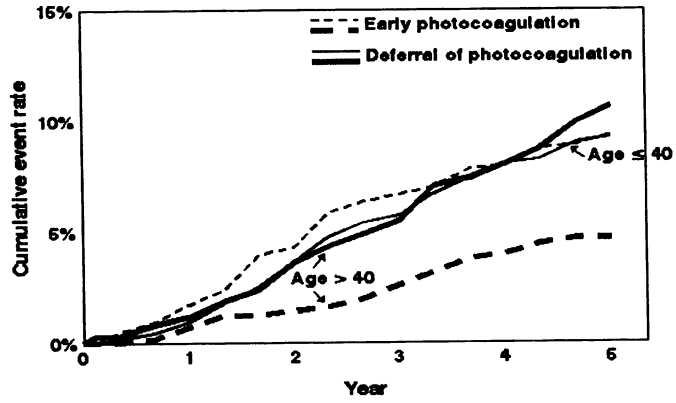
APPENDIX FIGURE 3

Development of severe visual loss or vitrectomy in early treated eyes compared with deferred eyes, for patients ≤ 40 years of age (p=0.19) and for patients > 40 years (p=0.0001). Test for interaction of treatment and age, p=0.05.



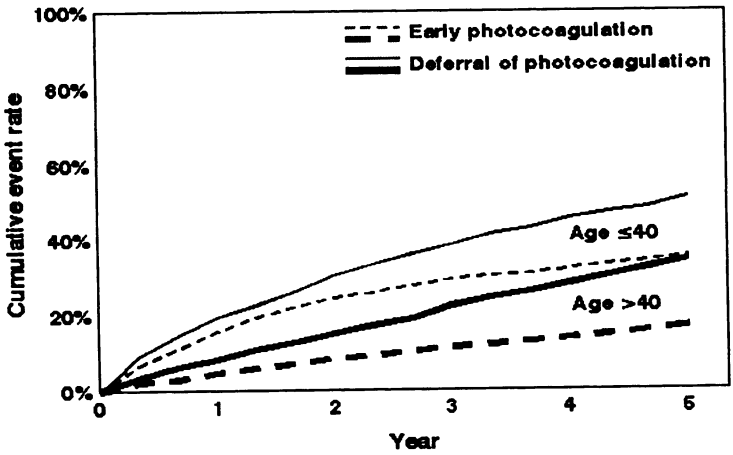
APPENDIX FIGURE 4A

Development of severe visual loss or vitrectomy in eyes with mild to moderate nonproliferative retinopathy at baseline. Early treated eyes compared with deferred eyes, for patients ≤ 40 years of age (p=0.01) and for patients > 40 years (p=0.02). Test for interaction of treatment and age, p=0.61.



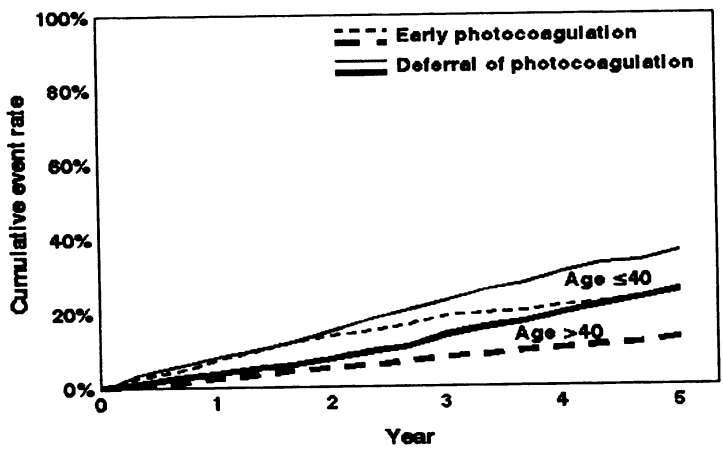
APPENDIX FIGURE 4B

Development of severe visual loss or vitrectomy in eyes with severe nonproliferative or early proliferative retinopathy at baseline. Early treated eyes compared with deferred eyes, for patients ≤ 40 years of age (p=0.87) and for patients > 40 years (p=0.0003). Test for interaction of treatment and age, p=0.25.



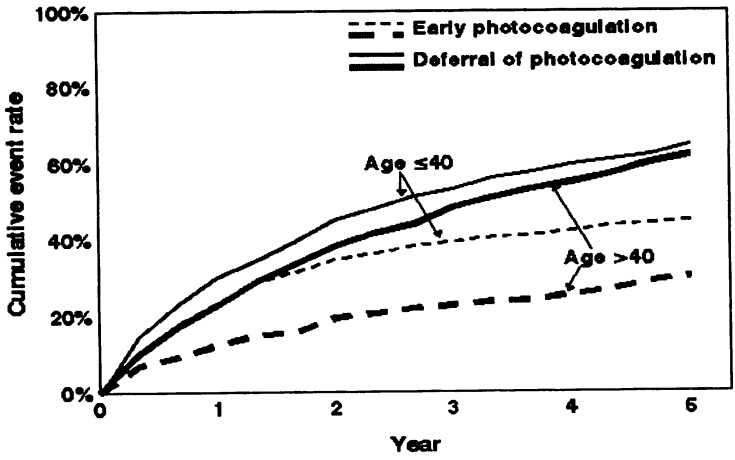
APPENDIX FIGURE 5

Development of high-risk proliferative diabetic retinopathy in early treated eyes compared with deferred eyes, for patients ≤ 40 years of age (p=0.0001) and for patients > 40 years (p=0.0001). Test for interaction of treatment and age, p=0.0005.



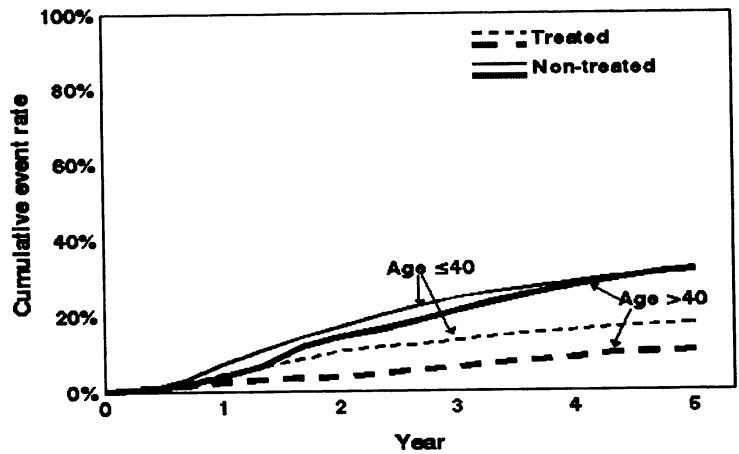
APPENDIX FIGURE 6A

Development of high-risk proliferative diabetic retinopathy in eyes with mild to moderate nonproliferative retinopathy at baseline. Early treated eyes compared with deferred eyes, for patients ≤ 40 years of age (p=0.0001) and for patients > 40 years (p=0.0001). Test for interaction of treatment and age, p=0.03.



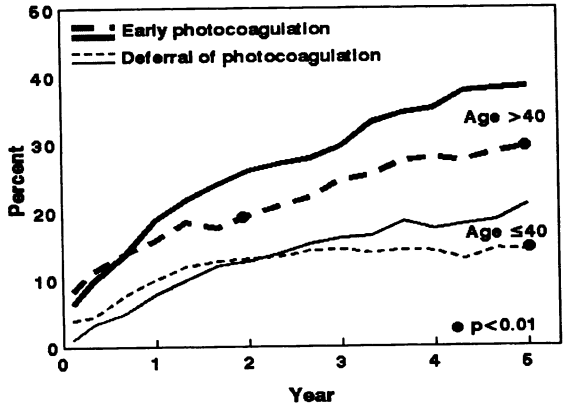
APPENDIX FIGURE 6B

Development of high-risk proliferative diabetic retinopathy in eyes with severe nonproliferative or early proliferative retinopathy baseline. Early treated eyes compared with deferred eyes, for patients ≤ 40 years of age (p=0.0001) and for patients > 40 years (p=0.0001). Test for interaction of treatment and age, p=0.002.



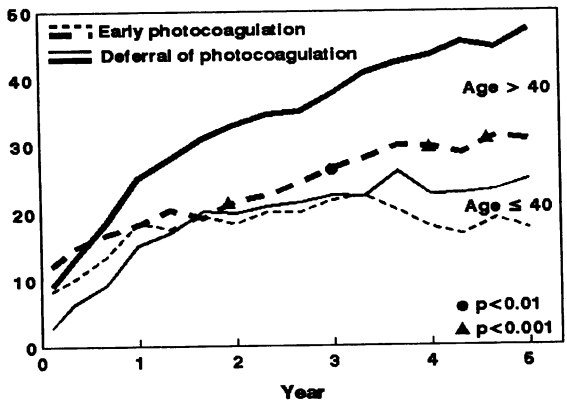
APPENDIX FIGURE 7

Development of severe visual loss in Diabetic Retinopathy Study. Treated eyes compared with nontreated eyes, for patients ≤ 40 years of age (p=0.0001) and for patients > 40 years (p=0.0001). Test for interaction of treatment and age, p=0.002.



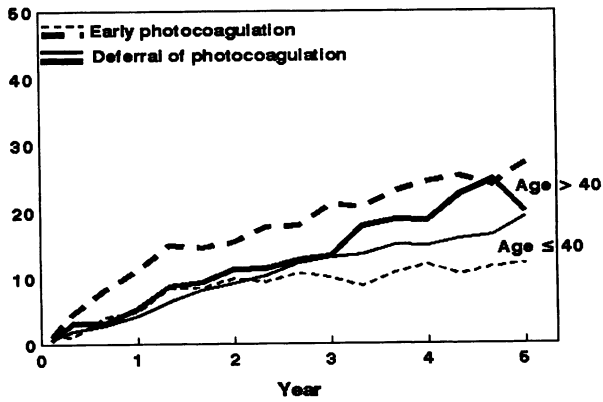
APPENDIX FIGURE 8

Proportion of eyes with decrease in visual acuity (doubling of visual angle) compared to baseline in eyes with severe nonproliferative or early proliferative retinopathy baseline, early treated eyes compared with deferred eyes, for patients ≤ 40 years of age and > 40 years. In younger age-group, significant treatment effect was observed at 5 years ($p<0.01$). In older age-group, significant treatment effects were observed at 2 and 5 years ($p<0.01$).



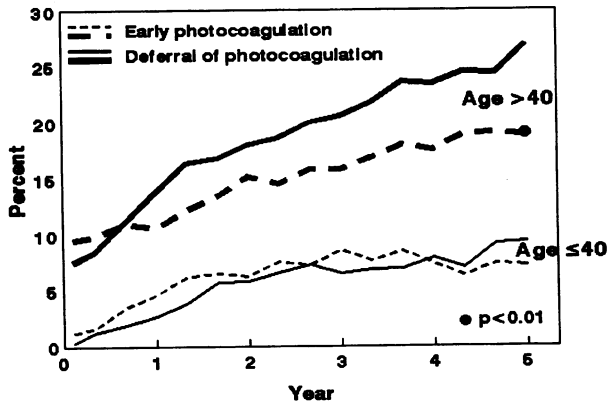
APPENDIX FIGURE 9A

Proportion of eyes with decrease in visual acuity (doubling of visual angle) compared to baseline in eyes with severe nonproliferative or early proliferative retinopathy baseline, early treated eyes compared with deferred eyes, for patients with clinically significant macular edema at baseline. In patients with type II diabetes, significant treatment effects were observed at 3 years ($p<0.01$) and 2, 4, and 5 years ($p<0.001$).



APPENDIX FIGURE 9B

Proportion of eyes with decrease in visual acuity (doubling of visual angle) compared to baseline in eyes with severe nonproliferative or early proliferative retinopathy baseline, early treated eyes compared with deferred eyes, for patients without clinically significant macular edema at baseline.



APPENDIX FIGURE 10

Proportion of eyes with visual acuity worse than 20/100 during follow-up in eyes with severe nonproliferative or early proliferative retinopathy baseline, early treated eyes compared with deferred eyes, for patients ≤ 40 years of age and > 40 years. In the older age-group, a significant treatment effect was observed at 5 years ($p<0.01$).