Early Worsening of Diabetic Retinopathy in the Diabetes Control and Complications Trial

The Diabetes Control and Complications Trial Research Group

Objectives: To document the frequency, importance of, and risk factors for “early worsening” of diabetic retinopathy in the Diabetes Control and Complications Trial (DCCT).

Methods: The DCCT was a multicenter, randomized clinical trial comparing intensive vs conventional treatment in insulin-dependent diabetic patients who had no to moderate nonproliferative retinopathy. Retinopathy severity was assessed in 7-field stereoscopic fundus photographs taken at baseline and every 6 months. For this study, worsening was defined as progression of 3 steps or more on the Early Treatment Diabetic Retinopathy Study final scale, as the development of clinically important retinopathy, or as any of the above, and was considered “early” if it occurred between baseline and 12-month follow-up visits.

Results: Early worsening was observed at the 6- and/or 12-month visit in 13.1% of 711 patients assigned to intensive treatment and in 7.6% of 728 patients assigned to conventional treatment (odds ratio, 2.06; P<.001); recovery had occurred at the 18-month visit in 51% and 55% of these groups, respectively (P=.39). The risk of 3-step or greater progression from the retinopathy level present 18 months after entry into the trial was greater in patients who previously had had early worsening than in those who had not. However, the large long-term risk reduction with intensive treatment was such that outcomes in intensively treated patients who had early worsening were similar to or more favorable than outcomes in conventionally treated patients who had not. The most important risk factors for early worsening were higher hemoglobin A1c level at screening and reduction of this level during the first 6 months after randomization. We found no evidence to suggest that more gradual reduction of glycemia might be associated with less risk of early worsening. Early worsening led to high-risk proliferative retinopathy in 2 patients and to clinically significant macular edema in 3; all responded well to treatment.

Conclusions: In the DCCT, the long-term benefits of intensive insulin treatment greatly outweighed the risks of early worsening. Although no case of early worsening was associated with serious visual loss, our results are consistent with previous reports of sight-threatening worsening when intensive treatment is initiated in patients with long-standing poor glycemic control, particularly if retinopathy is at or past the moderate nonproliferative stage. Ophthalmologic monitoring before initiation of intensive treatment and at 3-month intervals for 6 to 12 months thereafter seems appropriate for such patients. In patients whose retinopathy is already approaching the high-risk stage, it may be prudent to delay the initiation of intensive treatment until photocoagulation can be completed, particularly if hemoglobin A1c is high.


There have been many reports of the curious, unanticipated, and seemingly paradoxical worsening of diabetic retinopathy after rapid improvement of blood glucose control.1-18 Most of these reports have dealt with small groups of patients with insulin-dependent diabetes mellitus in whom worsening was observed within 3 to 12 months after initiation of intensive insulin treatment. In some cases worsening was striking and led to permanent visual impairment,16,17,18 while in others it was transient and apparently benign.7-15 Worsening appeared to be more frequent and/or more severe when retinopathy was more advanced and diabetes was of longer duration, and when improvement in control was greater or more rapid. In some reports worsening occurred more frequently in women.11,16,18 In this report we call this phenomenon early worsening (EW).

For editorial comment see page 931

The Diabetes Control and Complications Trial (DCCT) was a multicenter, randomized clinical trial designed to assess the benefits and risks of intensive as compared with conventional diabetes treatment in persons with insulin-dependent diabetes mellitus of 1 to 15 years’ duration and with retinopathy at baseline ranging from none to the moderate nonproliferative stage.19-22 The DCCT has previously published results that documented the remarkable, long-term beneficial effects of intensive treatment in re-
ASSESSMENT OF RETINOPATHY

Seven-field stereoscopic color fundus photographs were taken by certified photographers every 6 months and were graded centrally (with graders masked to treatment) according to the ETDRS modification of the Airlie House classification. This classification provides a grade for the severity of each type of lesion of diabetic retinopathy for each eye. Grades for the various lesions were used to derive overall retinopathy severity levels for each patient according to the ETDRS final scale.22

Fundus photographs were also obtained at 3 months for the initial 389 patients enrolled in the trial, after which this assessment was dropped from the protocol.

DEFINITIONS OF EW

In reports from other studies, worsening has been expressed variably as an increase of a specified amount along a severity scale,3,10,13,17 as the development of specific lesions such as soft exudates (SE; cotton-wool spots) and/or intraretinal microvascular abnormalities (IRMA; ie, dilated tortuous intraretinal vessels),11,13,15 and as clinically important progression with or without visual impairment.13,16,18 The time after initiation of intensive treatment at which worsening has been considered “early” has varied from 3 to 12 months.

We used 4 definitions of EW: (1) progression of 3 steps or more on the ETDRS final scale (3-step or more EW); (2) development of SE and/or IRMA in participants free of both lesions at baseline (SE/IRMA EW); (3) development of clinically important retinopathy, defined as severe nonproliferative diabetic retinopathy (SNPDR), proliferative diabetic retinopathy (PDR), or clinically significant macular edema (CSME), as defined in the ETDRS22 (clinically important EW); or (4) any EW, which was defined as present when any of the 3 other definitions of EW were present at a visit for a given patient. For each definition, EW was considered present if it was observed at the 6- and/or 12-month visit after randomization. The first 3 definitions are not mutually exclusive. The analysis of any 1 definition of EW included each patient who met the criteria for that definition, regardless of whether that patient also did or did not meet the criteria for other definitions of EW.

To evaluate the longer-term clinical impact of EW, we analyzed rates of subsequent progression from the level of retinopathy present at the 18-month visit, using the criterion of progression by 3 or more steps on the ETDRS final scale sustained for 2 consecutive 6-month visits (sustained 3-step progression).

BASELINE CHARACTERISTICS

Selected baseline characteristics stratified by baseline retinopathy severity level are shown in Table 1. In retinopathy severity level 10/10 (the primary intervention cohort), the shorter duration of diabetes and the lower AER reflected the lower maximum values required for eligibility in this cohort. Within the secondary intervention cohort (levels 20/<20 and higher), duration of diabetes, AER, and prevalence of clinical neuropathy increased with increasing retinopathy severity, as expected.

INCIDENCE OF AND RECOVERY FROM EW

The proportions of patients who experienced EW according to each definition at 6 and/or 12 months are presented in Table 2 together with the ORs for the intensive vs conventional treatment groups. More patients in the intensive treatment group experienced EW than in the conventional treatment group, particularly at the 6-month visit. The occurrence of 3-step or more EW at the 6-month visit was al-
of progression by 3 or more steps relative to the retinopathy level at 18 months, expressed as a rate per 100 patient-years, was computed separately for each of the 3 baseline retinopathy strata (10, 20s, or ≥30), and then for all the strata combined. The relative risk of 3-step or more progression for those with EW relative to those without EW was computed by means of the proportional hazards regression model, and the log relative risk (log hazard ratio) was estimated via the regression coefficients. These proportional hazards analyses were performed separately within baseline retinopathy strata, and then for all strata combined, both with and without stratifying for the levels of retinopathy at month 18.

The proportional hazards regression model was also used to compute the risk of 3-step or more progression in the intensive treatment group relative to the conventional treatment group, among those with EW and among those without EW by means of the Mann-Whitney test, separately for each of the 2 treatment groups. These analyses were performed with and without stratification adjustment for the baseline levels of retinopathy. In the stratified analysis, the overall test of differences between those with and those without EW was obtained with the Wei-Lachin test of stochastic ordering among the Mann-Whitney analyses within strata, using equal weights for each of the retinopathy strata. The data are summarized by presenting the proportion of patients whose retinopathy level at year 4 relative to the baseline level was better, the same, worse by 1 or 2 steps, or worse by 3 or more steps, separately among those with EW and among those without EW.

The differences between the intensive vs conventional treatment groups were also examined, separately among those with EW and among those without EW, by means of the Mann-Whitney test, with and without stratification for baseline retinopathy levels. The Wei-Lachin test was also used to test treatment group differences combined over strata and across those with and those without EW. Additionally, the Mann-Whitney difference between the groups was compared between those with EW and those without EW by means of a standard \( z \) test.

The subsequent event was counted at the time of the first of the 2 consecutive “positive” visits. We also compared change in retinopathy severity between the baseline and 4-year visits in those with vs those without EW.

**STATISTICAL METHODS**

Simple proportions were computed to describe the prevalence of the 4 types of EW within the intensive and conventional treatment groups, stratified by the baseline retinopathy severity level, and then for all the baseline levels combined. Within each baseline retinopathy stratum, a logistic regression model was used to compute the maximum likelihood estimate of the log odds of EW in the intensive treatment group relative to the conventional treatment group. Analyses were adjusted for baseline retinopathy level stratified according to whether there was no baseline retinopathy (10/10 on the ETDRS scale), microaneurysms only (20/20 or 20/20), or more severe retinopathy present (30/30 or worse).

The Wald chi-squared was used to assess the significance of individual regression coefficients, while the likelihood ratio chi-squared was used to assess the significance of the set of covariates simultaneously. The proportion of explained variation associated with a specific covariate is measured by the entropy (R\(^2\)), computed as the ratio of the likelihood ratio chi-squared to the \(-2 \log \text{likelihood of the model with no covariates.}^{25}\)

Analyses were also conducted comparing EW vs no EW and intensive vs conventional treatment within different subgroups based on selected baseline covariates. The homogeneity of odds ratios (ORs) for intensive vs conventional treatment among strata was tested by means of a treatment \( \times \) covariate interaction in the logistic model.

These regression models were used to describe the expected probability of EW as a function of the reduction in HbA\(_1c\) during the first 6 months of intensive therapy. The actual models included regression coefficients for the intercept (\( \beta_0 \)) and 13 covariates (\( \beta_1, \ldots, \beta_{13} \)). For an individual patient with covariate values (\( X_1, \ldots, X_{13} \)), the estimated probability of EW is provided by \( P = \left(1 + e^{-x \beta_0 + X_1 \beta_1 + \cdots + X_{13} \beta_{13}}\right)^{-1} \) where \( x = \beta_0 + X_1 \beta_1 + \cdots + X_{13} \beta_{13} \). In these models, \( X_1 \) is the value of the reduction in HbA\(_1c\) from screening to the average at months 4 and 5. To describe the average risk of EW as a function of the reduction in HbA\(_1c\), these estimated probabilities were obtained for a hypothetical patient with the average value of the other covariates.

For those with EW vs those without EW, the (crude) rate of progression was 3.5 times greater in the intensive than the conventional treatment group: 3.5% (25/711) vs 1.2% (9/728), OR = 2.98, \( P = .006 \). In the intensive group, 19 of these 25 cases had recovered to less than 3 steps worse at the next visit at month 12, while 6 of these 25 cases persisted. At the 12-month visit, 17 new cases were added, for a total of 23 (3.2%) in the intensive treatment group. In the conventional treatment group at 12 months, 5 of the 9 cases from 6 months had recovered, while 14 new cases were observed, for a total of 18 (2.5%). The total risk of 3-step or more EW at 6 and/or 12 months was 1.91 times greater in the intensive treatment group (\( P = .02 \)), owing largely to the excess of cases observed at 6 months. Total recovery at the 18-month visit was 69% in the intensive vs 57% in the conventional treatment group (OR = 1.56, \( P = .51 \)). These rates were similar to those observed at the subsequent visit when 3-step or more worsening from baseline occurred at any visit during follow-up, which were 72% and 31%, respectively; recovery at any future visit was 2.5 times as frequent with intensive as compared with conventional treatment (\( P < .01 \)).\(^{22}\) Similar patterns of greater risk in the intensive group were observed with SE/IRMA EW, OR = 2.41 (\( P < .001 \)); clinically important EW, OR = 1.57, \( P = .30 \); and with any EW, OR = 2.06 (\( P < .001 \)), while rates of recovery were similar in both treatment groups.

A similar analysis of any EW at the 3-month visit was conducted (data not shown) for the 389 patients who had 3-month photographs. The occurrence of any EW at the 3-month visit was 3.7 times greater in the intensive than the conventional treatment group: 10.7% (21/197) vs 3.6% (7/...
Table 3 presents the incidence and ORs of EW occurring at 6 or 12 months within subgroups of severity of retinopathy at baseline. Early worsening was most frequent when defined as development of SE/IRMA, and the frequency of this type of EW increased about 40-fold with increasing severity of baseline retinopathy. This steep increase was to be expected because development of SE/IRMA represents more substantial progression for eyes with no retinopathy than is the case for eyes that already have mild retinopathy. The percentage of patients with 3-step or more EW was substantially less than the percentage with SE/IRMA EW, and the occurrence of 3-step or more EW did not increase as markedly as a function of baseline retinopathy severity, at least in part because 3-step or more EW required a similarly steep increase.

IMPACT OF CLINICALLY IMPORTANT EW

Among the 25 cases of clinically important EW at 6 or 12 months, there were 3 eyes of 2 patients with high-risk PDR. Both patients had moderate NPDR at baseline and were in the intensive treatment group. All 3 eyes were treated with scatter photocoagulation and the new vessels regressed. The patient with high-risk PDR in both eyes, first observed at 3 months, also had CSME accompanied by a decrease in visual acuity to 20/40 in each eye, with partial recovery (to 20/25 in each eye) after focal/grid photocoagulation. In 3 additional patients (2 in the intensive and 1 in the conventional treatment group), CSME accompanied by decreases in visual acuity of 1 to 4 lines developed in 4 eyes (3 with mild and 1 with moderate NPDR at baseline), with recovery to 20/20 or better in 3 eyes and to 20/30 in the fourth (after focal/grid photoacoagulation in 2 eyes and spontaneous recovery in 2 eyes).

EW WITHIN RETINOPATHY SEVERITY SUBGROUPS

Table 3 presents the incidence and ORs of EW occurring at 6 or 12 months within subgroups of severity of retinopathy at baseline. Early worsening was most frequent when defined as development of SE/IRMA, and the frequency of this type of EW increased about 40-fold with increasing severity of baseline retinopathy. This steep increase was to be expected because development of SE/IRMA represents more substantial progression for eyes with no retinopathy than is the case for eyes that already have mild retinopathy. The percentage of patients with 3-step or more EW was substantially less than the percentage with SE/IRMA EW, and the occurrence of 3-step or more EW did not increase as markedly as a function of baseline retinopathy severity, at least in part because 3-step or more EW required a similarly steep increase.

INCIDENCE OF EW WITHIN OTHER SUBGROUPS

Table 4 presents the incidence of any EW with intensive vs conventional treatment within patient sub-
groups defined by baseline factors. In no instance was the OR for intensive vs conventional treatment significantly different between baseline subgroups (interaction $P=.10$). Among the like analyses for each definition of EW, only the difference between the ORs for SE/IRMA EW was nominally significant between men and women (1.6 in men vs 4.7 in women, $P = .03$, compared with 2.4 overall), excluding 23 women who were pregnant at 6 or 12 months (data not shown).

Table 4 also indicates that the risk of any EW increased significantly with increasing levels of screening HbA$_1c$ and duration of diabetes within both treatment groups, and with increasing levels of AER in the intensive treatment group.
PROGNOSTIC SIGNIFICANCE OF EW FOR SUBSEQUENT RETINOPATHY PROGRESSION

Figure 1 presents the cumulative incidence of sustained 3-step or more progression (ie, present at 2 or more consecutive 6-month visits) from the level present at the 18-month visit within each treatment group for patients who had and those who had not experienced 3-step or more EW. In the conventional treatment group, after an additional 5 years of follow-up, approximately 58% of those with 3-step or more EW would have subsequently experienced a further sustained progression of retinopathy, compared with 26% among those without such EW (Figure 1, left). In the intensive treatment group (Figure 1, right), approximately 20% of those with 3-step or more EW would have had subsequent progression, compared with 5% among those without such EW.

Table 5 presents rates of sustained 3-step or more progression of retinopathy from the level present at the 18-month visit for patients who had and those who had not experienced EW according to each definition. In addition to the crude rates, the adjusted relative risk of subsequent progression was computed comparing those with and those without previous EW, with adjustment for the actual level of retinopathy present at 18 months. For 3-step or more EW and SE/IRMA EW, in both treatment groups, progression rates were higher in participants who had experienced EW. Overall, the risk of subsequent progression was 1.9 to 4.1 times greater among those with 3-step or more EW or SE/IRMA EW; these relative risks were not significantly different between the treatment groups (data not shown).

For clinically important EW (Table 5), in the conventional treatment group, there was a similar 2-fold increase in risk of subsequent progression in participants with vs those without such EW, although this was not significant after adjusting for the level of retinopathy at 18 months. Within the intensive treatment group, there was no increased risk of subsequent progression among those with clinically important EW.

Comparison of rates of subsequent progression between the intensive and the conventional treatment groups (Table 5) shows the striking beneficial effect of intensive treatment, even in patients who experienced EW. Among those with 3-step or more EW (Table 5), the overall risks of subsequent progression with intensive and conventional treatment were 4.49 and 15.29 per 100 patient-years, respectively. The corresponding relative risk (intensive-conventional) is 0.35 (P = .03), which represents a 65% reduction in risk. Among those without 3-step or more EW, there was an 84% risk reduction with intensive treatment (1.04 vs 5.95 per 100 patient-years; P < .001). These risk reductions with intensive vs conventional treatment (65% vs 84%) are not significantly different (P = .12), which indicates that the relative benefit of intensive vs conventional treatment was not significantly different between those with and those without EW.

Table 4. Prevalence of Any Early Worsening and Odds Ratios for Intensive vs Conventional Treatment Within Subgroups Defined by Baseline Factors*

<table>
<thead>
<tr>
<th>Baseline Factor</th>
<th>Intensive</th>
<th>Conventional</th>
<th>Odds Ratio†</th>
<th>Interaction,‡ P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>No. (%) With Any EW</td>
<td>n</td>
<td>No. (%) With Any EW</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>366</td>
<td>48 (13)</td>
<td>394</td>
<td>35 (9)</td>
</tr>
<tr>
<td>Female§</td>
<td>335</td>
<td>43 (13)</td>
<td>321</td>
<td>18 (6)</td>
</tr>
<tr>
<td>Screening HbA1c</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;7.83</td>
<td>171</td>
<td>8 (5)</td>
<td>189</td>
<td>7 (4)</td>
</tr>
<tr>
<td>7.83-8.82</td>
<td>175</td>
<td>20 (11)</td>
<td>185</td>
<td>17 (9)</td>
</tr>
<tr>
<td>8.82-10.10</td>
<td>192</td>
<td>31 (16)</td>
<td>164</td>
<td>10 (6)</td>
</tr>
<tr>
<td>&gt;10.10</td>
<td>173</td>
<td>34 (20)</td>
<td>190</td>
<td>21 (11)</td>
</tr>
<tr>
<td>Duration, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5</td>
<td>412</td>
<td>18 (4)</td>
<td>443</td>
<td>9 (2)</td>
</tr>
<tr>
<td>≥5</td>
<td>299</td>
<td>75 (25)</td>
<td>285</td>
<td>46 (16)</td>
</tr>
<tr>
<td>AER, mg/24 h</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;15</td>
<td>480</td>
<td>51 (11)</td>
<td>480</td>
<td>33 (7)</td>
</tr>
<tr>
<td>15-40</td>
<td>192</td>
<td>32 (17)</td>
<td>213</td>
<td>19 (9)</td>
</tr>
<tr>
<td>&gt;40</td>
<td>39</td>
<td>10 (26) #</td>
<td>35</td>
<td>3 (9)</td>
</tr>
<tr>
<td>Neuropathy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>657</td>
<td>82 (12)</td>
<td>685</td>
<td>50 (7)</td>
</tr>
<tr>
<td>Yes</td>
<td>51</td>
<td>11 (22)</td>
<td>41</td>
<td>5 (12)</td>
</tr>
<tr>
<td>% of ideal body weight</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;120</td>
<td>638</td>
<td>84 (13)</td>
<td>641</td>
<td>47 (7)</td>
</tr>
<tr>
<td>≥120</td>
<td>73</td>
<td>9 (12)</td>
<td>87</td>
<td>8 (9)</td>
</tr>
</tbody>
</table>

*EW indicates early worsening; HbA1c, hemoglobin A1c; and AER, albumin excretion rate.
†For intensive vs conventional treatment, with 95% confidence intervals.
‡Test of equality of odds ratios across subgroups, eg, P = .13 for odds ratio of 1.66 in men vs 2.99 in women.
§Twenty-three pregnant women excluded (10 in the intensive group and 13 in the conventional group).
¶P < .001 for differences in percentage with any EW among subgroups.
#P < .05 for differences in percentage with any EW among subgroups.

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In fact, the risk of subsequent progression was significantly less among intensively treated patients with EW than among conventionally treated patients without EW for SE/IRMA EW (P = .03 for 1.78 vs 5.22 per 100 patient-years), clinically important EW (P = .03 for 1.39 vs 7.11 per 100 patient-years), and any EW (P < .01 for 2.33 vs 5.75 per 100 patient-years), but not for 3-step or more EW.

An alternate approach, which takes into consideration both the change occurring between baseline and 18 months and that occurring subsequently, is to consider the change between baseline and a fixed, long-term follow-up visit. For this purpose, we chose the change from baseline to 4 years, when the greatest number of subjects had long-term follow-up. Table 6 presents a summary of the distributions of the degree of change in retinopathy severity between the baseline and 4-year visits for participants with and without EW, according to each of the definitions. For participants with 3-step or more EW, mean change was about 4 steps worse in the conventional treatment group and about 2 steps worse in the intensive treatment group, compared with 1.1 and 0.6 steps worse, respectively, in these treatment groups among those without 3-step or more EW.

Analysis of the mean number of steps worse reflects the distance along the scale under the assumption of equal intervals of retinopathy severity between steps, but because the intervals cannot be assumed to be equal, statistical tests were not performed on the differences between these means. Instead, differences are presented between the EW and no EW groups in the estimated probability that participants in the specified group would have a less favorable outcome (more steps of worsening or fewer steps of improvement) compared with participants in the other group (the Mann-Whitney difference, EW − no EW). The Mann-Whitney difference is an appropriate statistic for use with the ordinal retinopathy se-

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**Table 5. Sustained 3-Step or More Progression From the Level of Retinopathy Observed at 18 Months With RR for Those With and Without Early Worsening Within Each Treatment Group, and With RR for Intensive vs Conventional Treatment Within Each Category of Early Worsening**

<table>
<thead>
<tr>
<th>Definition of Early Worsening</th>
<th>Treatment Group</th>
<th>Early Worsening</th>
<th>No Early Worsening</th>
<th>RR (E:N) (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>n Cases Person-Years Rate†</td>
<td>n Cases Person-Years Rate†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥3-Step</td>
<td>C</td>
<td>23 12 79 15.29</td>
<td>696 165 2774 5.95</td>
<td>1.93 (0.99-3.78)</td>
<td>&lt;.06</td>
</tr>
<tr>
<td></td>
<td>I</td>
<td>42 8 178 4.49</td>
<td>660 31 2968 1.04</td>
<td>3.24 (1.34-7.85)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>RR (I:C) = 0.35</td>
<td>95% CI = 0.14-0.88</td>
<td>P &lt; .03</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SE/IRMA</td>
<td>C</td>
<td>36 14 129 10.85</td>
<td>618 130 2493 5.22</td>
<td>2.34 (1.17-4.68)</td>
<td>&lt;.02</td>
</tr>
<tr>
<td></td>
<td>I</td>
<td>71 6 337 1.78</td>
<td>577 21 2567 0.82</td>
<td>4.05 (1.12-14.7)</td>
<td>&lt;.03</td>
</tr>
<tr>
<td>RR (I:C) = 0.18</td>
<td>95% CI = 0.07-0.48</td>
<td>P &lt; .001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinically important‡</td>
<td>C</td>
<td>11 7 35 20.00</td>
<td>334 101 1421 7.11</td>
<td>2.01 (0.81-5.02)</td>
<td>&lt;.13</td>
</tr>
<tr>
<td></td>
<td>I</td>
<td>14 1 72 1.39</td>
<td>342 27 1686 1.60</td>
<td>0.41 (0.05-3.24)</td>
<td>&lt;.40</td>
</tr>
<tr>
<td>RR (I:C) = 0.14</td>
<td>95% CI = 0.02-1.19</td>
<td>P &lt; .07</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any early worsening</td>
<td>C</td>
<td>54 24 190 12.66</td>
<td>665 153 2863 5.75</td>
<td>1.81 (1.09-3.01)</td>
<td>&lt;.02</td>
</tr>
<tr>
<td></td>
<td>I</td>
<td>93 10 430 2.33</td>
<td>609 29 2717 1.07</td>
<td>1.59 (0.67-3.78)</td>
<td>&lt;.30</td>
</tr>
<tr>
<td>RR (I:C) = 0.20</td>
<td>95% CI = 0.09-0.43</td>
<td>P &lt; .001</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* RR indicates relative risk; E:N, early worsening vs no early worsening; CI, confidence interval; C, conventional; I, intensive; SE, soft exudates; and IRMA, intraretinal microvascular abnormalities. Adjusted relative risk is stratified by retinopathy level at 18 months according to the following categories: 10/10, 20/20, 20/20, 35/35, 35/35, and 43/43+.
† Rate per 100 person-years.
‡ Secondary intervention cohort only.

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Figure 1. Cumulative incidence of sustained 3-step or more progression from the level of retinopathy present at 18 months for those with and those without 3-step or more early worsening. Left, Conventional treatment group. Right, Intensive treatment group.
For 3-step or more EW, the Mann-Whitney difference (stratified-adjusted for baseline retinopathy category) was 0.63 in the conventional treatment group and 0.54 in the intensive treatment group, indicating substantially greater probability of retinopathy progression between baseline and 4 years in patients with EW in both treatment groups. The difference between the 2 treatment groups was not significant (P = .38).

Likewise, there was more progression in participants with than in those without SE/IRMA EW. The increase in the degree of progression among those with vs without SE/IRMA EW was smaller in the intensive than in the conventional treatment group (P = .04 for 0.63 vs 0.45). Most clinically important EW occurred in the most severe baseline retinopathy category (Table 3) and was associated with a less favorable outcome at the 4-year visit only in the conventional treatment group (Table 6) (overall, P < .001 for Mann-Whitney difference of 0.79 in the conventional group vs 0.14 in the intensive group). Among those with such clinically important EW in the intensive group, 62% (8/13) recovered at 4 years to a level the same as or better than that at baseline, vs 18% (2/11) of those in the conventional group.

As with 3-step or more EW and SE/IRMA EW, in both treatment groups, those with any EW had a less favorable retinopathy status at 4 years than those without any EW; the difference between treatment groups was not significant (P = .38 for 0.49 vs 0.34).

**BASELINE PREDICTORS OF EARLY WORSENING**

Table 7 presents logistic regression models for the risk (OR) of any EW as a function of a set of baseline characteristics (selected a priori) separately for the intensive and conventional treatment groups. Since the results were similar for each type of EW, only the models for any EW are presented. Within each treatment group, the screening (before randomization) level of HbA_1c was among the most important predictors of EW, as reflected by the relative magnitude of the R^2 value for each covariate. The increased risk associated with more severe retinopathy at baseline was contributed mostly by cases of SE/IRMA EW (as expected from Table 3). The risk of EW also tended to increase with increasing duration of diabetes (in both cohorts and both treatment groups) and to decrease in women in the conventional treatment group.

**REDUCTION IN HbA_1c LEVEL AND RISK OF EW**

Figure 2 shows the distribution of the change in HbA_1c level from the screening visit to the 6-month visit in each treatment group. In the conventional treatment group, the level of HbA_1c remained relatively unchanged; more than 60% were within 0.2 of their initial level and less than 10% had a reduction of 2 or more HbA_1c percent. In the intensive treatment group, the levels of HbA_1c fell rapidly during the first 3 months of treatment.
Conventional

At the 6-month visit, the median reduction in HbA1c level from the value at screening was 1.8, with lower and upper quartiles of 1.0 and 3.0 HbA1c percent. The change in HbA1c level from screening to 6 months, however, was highly associated with the initial screening value; those entering the trial with the highest screening HbA1c values experienced the greatest reduction in HbA1c with intensive therapy.

Crude rates of any EW are depicted in Figure 3 as a function of the tertiles of screening HbA1c values, and within these, in tertiles of the month 6 reduction in HbA1c. As the figure is scanned from front to back, examining increasing reductions in HbA1c among subgroups with similar screening HbA1c levels, rather steep increases in the incidence of EW are seen. Scanning across the figure from right to left, examining increasing levels of HbA1c at screening among subgroups with similar reductions, there are less steep and less consistent increases in the incidence of EW. Even though the reductions in HbA1c were not as great among conventionally treated patients, the crude risks of EW in this treatment group appeared comparable with those in intensively treated patients who had equivalent reductions in HbA1c.

The relationships of EW to screening HbA1c and reduction of HbA1c during the first 6 months of treatment were further explored by means of logistic regression models. Since the screening HbA1c is included in these models, the estimated OR, P value, and R² values will be identical for the effect of an individual follow-up HbA1c value (eg, at month 3) and that of the change from the screening HbA1c (eg, from screening to month 3). Models in the conventional treatment group showed that the reduction in HbA1c at the 3- and 6-month visits, either individually or in aggregate, did not add significantly (P>.88) to the contribution of the screening HbA1c.
other baseline covariates to the risk of either 3-step or more EW or SE/IRMA EW.

Initial models in the intensive group examined the effects of the HbA1c values at each month (months 1-6), when adjusted for the other baseline covariates. In combination, the first 6 monthly HbA1c levels added significantly to the model for the risk of 3-step or more EW (P = .05) and to the model for SE/IRMA EW (P = .006), but not to the model for clinically important EW (P = .33). The effects of these HbA1c measures were also examined individually and in various combinations, including the slope of the decrease during the first 3 months and during the entire 6 months. Of these, the month 4 and month 5 HbA1c values accounted for most of the association with the risk of 3-step or more EW and SE/IRMA EW. Therefore, subsequent analyses used the mean of the month 4 and 5 values for each subject, designated as the month 4-5 value. We then explored the relative contributions of the screening HbA1c, the month 4-5 value, and the change in HbA1c from screening to month 4-5. Of these, the change from screening to month 4-5 was most important.

Models that include the screening HbA1c and change from screening to month 4-5, in addition to the other baseline covariates, are presented in Table 8 for the risks of 3-step or more EW, SE/IRMA EW, and any EW in the intensive treatment group. Comparison of the any EW panel with the intensive treatment group model in Table 7 shows results that are almost identical, except that the reduction in HbA1c has replaced the screening HbA1c value as an important risk factor. The effect of screening HbA1c is not significant because this effect is in part absorbed into the effect of the change at months 4-5, which depends on the screening value itself. For those with a screening HbA1c level of 7%, the range of HbA1c reductions at month 4-5 spanned only 0% to 2%, while the range for those with a screening HbA1c of 10% spanned 0% to 4.6% (2% and 4.6% being the 95th percentiles of the respective distributions of reduction of HbA1c).

In these models, for each unit decrease in mean HbA1c percentage at month 4-5 from the value at screening, there was a 1.6-fold increase in the risk of any EW, a 1.5-fold increase in the risk of 3-step or more EW, and a 1.7-fold increase in the risk of SE/IRMA EW. This risk gradient for 3-step or more EW is depicted in Figure 4, left, separately for the primary and secondary cohorts. The corresponding risk gradients for SE/IRMA EW are presented in Figure 4, right. Each figure is based on the means of the covariate values. For a patient with different values of the other covariates, the risks (odds) of EW would be proportional to those presented in the figures.

Although the goal for all patients assigned to intensive treatment was the rapid achievement of normoglycemia, there was considerable variability in the time course of the reduction in HbA1c, occurring between the initial screening, baseline evaluation, and 6-month visits in both intensively and conventionally treated patients. Therefore, post hoc, we compared the incidence of EW in groups of patients whose HbA1c level decreased at different rates. We calculated reductions in each of 3 time intervals (screening to baseline, baseline to month 3, and month 3 to month 6), summed these reductions (ignoring any increases), and cross-classified patients by the total reduction in HbA1c and by the time course of the reduction. For convenience, and to provide adequate numbers in each cell, total reduction was divided into intervals that approximated 2 to 3, 3 to 4, and 4 or more HbA1c reduction (1.75-2.74%, 2.75-3.74%, and 3.75%).

Table 8. Logistic Regression Analysis of Odds of Early Worsening as a Function of Baseline Covariates and Change in HbA1c: Intensive Treatment

<table>
<thead>
<tr>
<th>Covariates</th>
<th>OR (95% CI)</th>
<th>P</th>
<th>R², %</th>
<th>OR (95% CI)</th>
<th>P</th>
<th>R², %</th>
<th>OR (95% CI)</th>
<th>P</th>
<th>R², %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening HbA1c 1% higher</td>
<td>1.19 (0.83-1.71)</td>
<td>.34</td>
<td>0.28</td>
<td>1.10 (0.77-1.56)</td>
<td>.61</td>
<td>0.06</td>
<td>1.12 (0.84-1.49)</td>
<td>.45</td>
<td>0.10</td>
</tr>
<tr>
<td>Neuropathy vs not</td>
<td>1.52 (0.56-4.13)</td>
<td>.41</td>
<td>0.22</td>
<td>1.42 (0.50-4.00)</td>
<td>.51</td>
<td>0.10</td>
<td>0.82 (0.35-1.89)</td>
<td>.64</td>
<td>0.04</td>
</tr>
<tr>
<td>Female vs male</td>
<td>0.76 (0.38-1.51)</td>
<td>.43</td>
<td>0.19</td>
<td>1.05 (0.57-1.93)</td>
<td>.87</td>
<td>0.01</td>
<td>0.96 (0.59-1.59)</td>
<td>.87</td>
<td>0.00</td>
</tr>
<tr>
<td>% of ideal body weight 1% higher</td>
<td>0.98 (0.95-1.01)</td>
<td>.25</td>
<td>0.42</td>
<td>0.97 (0.95-1.01)</td>
<td>.07</td>
<td>0.74</td>
<td>0.98 (0.96-1.00)</td>
<td>.12</td>
<td>0.43</td>
</tr>
<tr>
<td>Primary cohort</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AER higher by 1 mg/24 h</td>
<td>0.99 (0.94-1.04)</td>
<td>.08</td>
<td>0.05</td>
<td>0.99 (0.93-1.06)</td>
<td>.82</td>
<td>0.01</td>
<td>0.99 (0.94-1.04)</td>
<td>.70</td>
<td>0.03</td>
</tr>
<tr>
<td>Duration higher by 1 y</td>
<td>1.41 (1.01-1.98)</td>
<td>.04</td>
<td>1.30</td>
<td>1.77 (1.12-2.78)</td>
<td>.01</td>
<td>1.34</td>
<td>1.42 (1.02-1.99)</td>
<td>.04</td>
<td>0.78</td>
</tr>
<tr>
<td>Secondary cohort</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AER higher by 1 mg/24 h</td>
<td>0.99 (0.98-1.01)</td>
<td>.58</td>
<td>0.10</td>
<td>1.00 (0.98-1.01)</td>
<td>.53</td>
<td>0.09</td>
<td>1.00 (0.99-1.01)</td>
<td>.55</td>
<td>0.07</td>
</tr>
<tr>
<td>Duration higher by 1 y</td>
<td>1.18 (1.03-1.35)</td>
<td>.02</td>
<td>1.69</td>
<td>1.17 (1.05-1.31)</td>
<td>.004</td>
<td>1.86</td>
<td>1.19 (1.07-1.31)</td>
<td>.001</td>
<td>2.05</td>
</tr>
<tr>
<td>20/20 vs 10/10</td>
<td>1.39 (0.23-8.44)</td>
<td>.72</td>
<td>0.04</td>
<td>26.89 (2.39-302)</td>
<td>.008</td>
<td>1.58</td>
<td>2.45 (0.51-11.6)</td>
<td>.26</td>
<td>0.23</td>
</tr>
<tr>
<td>20/20 vs 10/10</td>
<td>1.75 (0.24-13.0)</td>
<td>.59</td>
<td>0.09</td>
<td>63.01 (5.21-762)</td>
<td>.001</td>
<td>2.36</td>
<td>5.06 (0.97-26.3)</td>
<td>.05</td>
<td>0.68</td>
</tr>
<tr>
<td>35+ vs 10/10</td>
<td>0.67 (0.07-6.44)</td>
<td>.73</td>
<td>0.04</td>
<td>189.5 (14.7-2422)</td>
<td>.001</td>
<td>3.60</td>
<td>10.49 (19.1-57.7)</td>
<td>.007</td>
<td>1.33</td>
</tr>
<tr>
<td>43+ vs 10/10</td>
<td>2.16 (0.22-21.7)</td>
<td>.51</td>
<td>0.13</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>3.84 (0.57-26.1)</td>
<td>.17</td>
<td>0.34</td>
</tr>
<tr>
<td>Reduction in HbA1c from screening to months 4-5 greater by 1%</td>
<td>1.47 (1.02-2.12)</td>
<td>.04</td>
<td>1.31</td>
<td>1.69 (1.18-2.43)</td>
<td>.004</td>
<td>1.81</td>
<td>1.60 (1.19-2.15)</td>
<td>.002</td>
<td>1.77</td>
</tr>
</tbody>
</table>

*HbA1c indicates hemoglobin A1c; EW, early worsening; SE, soft exudates; IRMA, intraretinal microvascular abnormalities; OR, odds ratio; CI, confidence interval; AER, albumin excretion rate; and ND, not determined.
†Model X² = 49.43, R² = 15.51.
‡Model X² = 164.92, R² = 36.69.
§Model X² = 138.75, R² = 25.19.
With these definitions, 80% of the 258 patients in the shorter interval category had 80% or more of their total reduction in the baseline to month 3 interval, while 22% of the 170 patients in the longer interval category had their total reductions spread fairly evenly across all 3 intervals (ie, had $\leq 20\%$ of the total in each interval) and nearly all of the remainder had 80% or more of the reduction spread across 2 adjacent intervals (screening to 3 months in 42% and baseline to 6 months in 44%).

Table 9 presents the proportions of patients (intensive and conventional treatment groups combined) in each of the resulting 9 subgroups who developed any EW. There was no consistent relationship between the rapidity of HbA1c decrease and the frequency of EW.

**COMMENT**

**PROGNOSTIC IMPORTANCE OF EW**

The risk of further sustained 3-step or more progression from the retinopathy level present at 18 months was 2 to 4 times greater in patients who had had 3-step or more EW or SE/IRMA EW vs those who had not (Table 5). However, the large risk reduction of intensive vs conventional treatment observed overall was present to a similar degree among those who developed EW and those who did not. For SE/IRMA EW, clinically important EW, and any EW, the long-term risk of progression in intensively treated patients who developed EW was actually less than that in conventionally treated patients who did not. An analysis of change in retinopathy between the baseline and 4-year visits also showed more progression in patients with EW than in those without it when comparisons are made within treatment groups, as well as less progression in the intensive vs the conventional treatment groups when comparisons were made among those with and those without EW (Table 6). However, in this analysis, outcome in intensively treated patients who developed EW tended to be similar to that in conventionally treated patients who did not. Thus, the phenomenon of EW indicates a poorer retinopathic prognosis, yet one that can still be greatly mitigated by long-term intensive treatment.

**RISK FACTORS FOR EW**

The most consistent baseline risk factor for EW was the screening level of HbA1c obtained at the initial contact with each patient (OR for any EW of 1.6 for each unit increase).
increase in HbA1c percent at screening in the intensive treatment group and 1.3 in the conventional treatment group; Table 7).

The decrease in HbA1c during the first 6 months of intensive treatment was also a risk factor for 3-step or more EW and SE/IRMA EW. It was difficult to separate this effect from that of the screening level of HbA1c because the decrease was greatest in patients who entered with the highest levels at screening. Thus, a higher initial value of the screening HbA1c was associated with a greater reduction in HbA1c, which in turn was associated with increased risk of EW (Figure 3). In the conventional treatment group, few patients experienced a substantial decrease in HbA1c (Figure 2), and in this group the levels of HbA1c during the first 6 months of the trial did not add significantly to the screening HbA1c and other risk factors in predicting EW (data not shown). In the intensive treatment group, regression analyses incorporating both screening HbA1c and change between the screening and month 4-5 values showed the latter to be the dominant risk factor for 3-step or more EW and SE/IRMA EW (Table 8). Overall, after adjusting for the screening level of HbA1c and other factors, for every unit reduction in HbA1c percent at month 4-5 with intensive therapy, there was a 47% increase in the odds of 3-step or more EW and a 69% increase in the odds of SE/IRMA EW.

Others have also found the level of hyperglycemia at baseline and the magnitude of its reduction after improved control to be the predominant risk factors for EW,7,11,14,15,17,18 and the suggestion has frequently been made that the risk might be decreased by improving control more slowly. We could not address this question directly (to do so would require a randomized study), but we were able to compare the incidence of EW in those patients who experienced nearly all of the reduction in the first 3 months after baseline with those in whom the reduction was spread across an interval of 6 to 9 months, simultaneously controlling for the total amount of reduction in HbA1c. In this analysis, we found no evidence to support the suggestion that HbA1c reduction across a longer interval was associated with less risk of EW than a reduction during a shorter interval, when the reductions were of comparable magnitude. Moreover, in the regression models, the slope of the decrease in HbA1c during the first 3 or 6 months of treatment was a less powerful predictor of EW than was the month 4-5 level.

CLINICALLY IMPORTANT EW

The cases we have classified as clinically important EW were similar to those observed in other clinical trials that included patients with moderate NPDR in that progression, though clinically important, was not catastrophic.7,12 High-risk PDR developed in only 3 eyes, all of which responded well to scatter photocoagulation. In 6 eyes CSME led to small decreases in visual acuity, with recovery to 20/20 or better in 3 eyes, to 20/25 in 2, and to 20/30 in 1. Others have reported case series in which there was more serious progression, sometimes leading to substantial loss of vision.4,16,15,13,18 The cases in each of these reports differed from those in the DCCT and similar trials in that retinopathy was more severe and/or blood glucose control was poorer at baseline (and thus the decrease after initiation of intensive insulin treatment was greater).

PATHOGENESIS OF EW

Although our analyses provide strong documentation of the importance of the magnitude of the decrease in HbA1c, as a risk factor for EW (Figure 4 and Table 8), they do not advance the debate regarding the specific pathogenesis of EW. Early worsening tended to occur earlier (Table 2) and recovery from it to be more frequent (Tables 2 and 5) in intensively treated than in conventionally treated patients, but we found no other distinguishing features. Possible mechanisms of EW suggested by others have included decrease in nutrient substrate, decreased ability of the retinal circulation to autoregulate, and increase in growth factors.11,31-34

In our analyses the magnitude, but not the rapidity, of the reduction in HbA1c during the first 6 months of intensive treatment was an important risk factor for EW. Intensive treatment led to an approximately 2-fold increase in the risk of EW (Table 3), which in turn increased the risk of subsequent retinopathy progression 2- to 4-fold (Table 5). However, the remarkable ultimate beneficial effect of long-term intensive treatment outweighed these risks, so that retinopathy progression between the baseline and 4-year visits was no greater even in intensively treated patients who experienced EW than in conventionally treated patients who did not, and the risk of progression from the retinopathy level present at the 18-month visit tended to be less in the former group than in the latter. Thus, as previously recommended,21 intensive treatment should be implemented in all appropriate patients, with the expectation that the long-term risks of retinopathy progression, and the risks of the other microvascular complications of insulin-dependent diabetes mellitus, will be substantially reduced.

However, whereas no case of EW was associated with serious visual loss in the DCCT, our results are consistent with previous reports of the occurrence of sight-threatening worsening when intensive treatment is initiated in patients with long-standing poor glycemic control, particularly if retinopathy is at or past the moderate nonproliferative stage.4,16,15,13,18 Ophthalmologic monitoring before initiation of intensive treatment and at 3-month intervals for 6 to 12 months thereafter would seem to be appropriate for such patients. In patients whose retinopathy is already approaching the high-risk stage (very severe NPDR or early PDR), it may be prudent to delay the initiation of intensive treatment until photocoagulation can be completed, particularly if HbA1c level is high and a large reduction is anticipated.

Accepted for publication February 5, 1998.

The DCCT is sponsored by the Division of Diabetes, Endocrinology, and Metabolic Diseases of the National Institutes of Diabetes and Digestive and Kidney Diseases, the National Institutes of Health, Bethesda, Md, through coop-
References


Be sure to visit the Archives of Ophthalmology’s World Wide Web site (http://www.ama-assn.org/ophth) and try your hand at our new Clinical Challenge interactive quiz. We invite visitors to make a diagnosis based on selected information from a case report or other feature scheduled to be published in the following month’s print edition of the Archives. The first visitor to e-mail our Web editors with the first correct answer wins an Archives of Ophthalmology CD-ROM and will be recognized in the print journal and on our Web site. A full discussion of the case featured in the quiz can be found in the following month’s print edition of the journal.

Archives Web Quiz Winner for June 1998:
Our congratulations to the winner of our Clinical Challenge, Christina Muccioli, MD, Paulista School of Medicine, Federal University of São Paulo, São Paulo, Brazil.
tomic space for this kind of hemorrhage.\textsuperscript{14,18} The presence of a glistening light reflex and fine striae on the surface of the hemorrhage upon funduscopic examination may indicate involvement of the internal limiting membrane. It is believed that in cases with Terson syndrome and Valsalva retinopathy, the premacular hemorrhage occurs beneath the internal limiting membrane.\textsuperscript{6,7,19} From our clinical observation, the exact location of the premacular subhyaloid hemorrhage is impossible to determine biomicroscopically. Therefore, we refused to use terms specifying anatomical layers, such as “photodisruption of the hemorrhagic detachment of the internal limiting membrane” or “posterior hyaloidotomY.”\textsuperscript{1,6,11,12,14,15}

In our series, a retinal detachment occurred as a complication in 1 patient with bilateral myopia and associated retinal breaks, but retinal breaks occurred in his un-treated fellow eye as well. Peri-retinal breaks and retinal detachment are also a well-recognized complication of Nd:YAG laser capsulotomy after cataract surgery.\textsuperscript{20-22} The macular hole identified after Nd:YAG laser treatment in a young woman with Valsalva retinopathy was another complication. Possibly the photodisruptive effect was too close to the macula. The trapped blood is believed to act as a cushion, dampening the disruptive impact of the Nd:YAG laser burst, as indicated by visible fluid waves. In a small hemorrhage, the laser burst occurs close to the macula, and the protective dampening effect may be insufficient. Although a macular hole was observed neither in the other eyes with more extended hemorrhages that were treated nor in eyes treated by other authors,\textsuperscript{1,5,6,11-16} this serious complication clearly limits the safety of the procedure. This may be important for small premacular subhyaloid hemorrhage, which is considered self-limiting.\textsuperscript{7} Therefore, from our experience, we advocate laser drainage only if the size of the hemorrhage is beyond 3 disc diameters. Precise focusing of the surface of the hemorrhage seems to be important, too, and we do not exceed energies of 9 mJ for safety reasons.\textsuperscript{20}

In conclusion, Nd:YAG laser treatment may be considered for recent premacular subhyaloid hemorrhage beyond 3 disc diameters in diameter. Clinical benefits include rapid visual rehabilitation, visualization of the underlying retina, expedited access for macular photocoagulation, and the avoidance of vitrectomy in two thirds of cases. Further long-term surveillance of laser-treated cases is necessary, and only randomization with deferral of treatment or vitrectomy can define benefits and disadvantages.

Accepted for publication July 29, 1998.

This study was supported by The Royal Society, London, England (623/008.F621/DHG/LM, Dr Ulbig) and Deutsche Forschungsgemeinschaft DFG, Bonn, Germany (Ul 109/1-1, Dr Ulbig).

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REFERENCES


Correction

Error in Figure. In the article titled “Early Worsening of Diabetic Retinopathy in the Diabetes Control and Complications Trial,” published in the July 1998 issue of the ARCHIVES (1998;116:874-886), an error appeared in Figure 4 on page 884. The key explaining the solid and dashed lines should not have appeared in the figure. The solid and dashed lines are correctly defined in the figure legend. The journal regrets the error.