How Many Steps of Progression of Diabetic Retinopathy Are Meaningful?

The Wisconsin Epidemiologic Study of Diabetic Retinopathy

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Objective: To determine whether a 1-step or more or 2-step or more progression on the Early Treatment Diabetic Retinopathy Study retinopathy severity scale over a 4-year period is meaningful in predicting the subsequent incidence of proliferative diabetic retinopathy (PDR) and clinically significant macular edema (CSME) over the following 6 years.

Design: Population-based study of diabetic persons with 10 years of follow-up.

Setting and Patients: Eleven-county area in southern Wisconsin. There were 1025 persons with diabetes who had fundus photographs at baseline and at 4- and 10-year follow-up examinations.

Main Outcome Measures: Incidence of PDR or CSME between the 4- and 10-year follow-up examinations as determined by masked grading of color stereoscopic fundus photographs of 7 standard fields.

Results: In a univariate analysis, those with 1 or more steps of progression (n=551) over the first 4 years of the study were significantly (P<.0001) more likely to develop PDR over the next 6 years than those with no progression (n=474) (26% vs 4%) (relative risk, 5.85; 95% confidence interval, 4.05-8.47). Similarly, those with 2 or more (n=364) (33%) or 3 or more (n=231) (41%) steps of progression over the first 4 years of the study were significantly (P<.0001) more likely to develop PDR over the next 6 years than those with lesser progression (n=661 [7%] and n=794 [9%], respectively) (relative risk, 5.10; 95% confidence interval, 3.83-6.80; and relative risk, 4.61; 95% confidence interval, 3.57-5.99, respectively). Similar associations were apparent at every level of retinopathy, duration of diabetes, and glycated hemoglobin, and by type of diabetes at baseline. There were also associations between retinopathy progression and incidence of CSME.

Conclusions: It seems that 1 or more or 2 or more steps of progression of retinopathy over a 4-year period strongly predict the development of PDR over the next 6 years. Therefore, using these end points of progression would result in the need for fewer subjects or shorter follow-up in some clinical trials.

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Reduction in the incidence of proliferative diabetic retinopathy (PDR), clinically significant macular edema (CSME), and substantial loss of vision have served as primary end points in randomized clinical trials of treatment for diabetic retinopathy.1-3 Data from epidemiologic studies show that over a 10-year period these end points have a low incidence in people with no or minimal diabetic retinopathy at the beginning of the observation interval.4 For this reason, other clinically meaningful measures of progression of retinopathy, such as 2- or 3-step progression on the Early Treatment Diabetic Retinopathy Study (ETDRS) severity scale, have been used as primary end points in clinical trials testing the efficacy of intensive hypoglycemic treatment in patients with no or minimal diabetic retinopathy.5,6 These trials required large numbers of subjects followed up for many years. Trials designed to test the efficacy of new treatments for primary prevention may not always be feasible because of the length of time required and the large number of subjects needed. For this reason, other end points that are associated with development of severe disease outcomes in the future, such as change in retinal microaneurysm counts, have been suggested for use in these trials.7,8 There are few studies that actu-
PATIENTS AND METHODS

A population-based sample of 2990 persons was selected for examination. The sample was composed of 2 groups. The first group consisted of all patients diagnosed as having diabetes before the age of 30 years and taking insulin (n=1210); this group will be referred to as “younger onset.” The second group consisted of a probability sample of patients whose conditions were diagnosed when they were 30 years or older. Their diagnosis had been confirmed by a random or postprandial serum glucose level of at least 11.1 mmol/L, or a fasting serum glucose level of at least 7.8 mmol/L on at least 2 occasions (n=1780); this group will be referred to as “older onset.” Of the older-onset group, 824 were taking insulin and 956 were not. Participants from both the younger- and older-onset groups contribute data to subsequent analyses.

Baseline (1980-1982) and follow-up (1984-1986 and 1990-1992) examinations were conducted using standardized protocols. Pertinent parts of the ocular and physical examination included measuring blood pressure, dilating the pupils, administering a medical history questionnaire, taking stereoscopic color fundus photographs of 7 standard fields and a nonstereoscopic red reflex photograph of each eye, and determining glycosylated hemoglobin values.

To determine retinopathy status at both the baseline and follow-up examinations, all fundus photographs were graded using a modification of the Airlie House classification scheme that specified the following levels of retinopathy for each eye: (1) level 10: no retinopathy; (2) level 21: microaneurysms only or retinal hemorrhages of soft exudates in the absence of microaneurysms; (3) level 31: microaneurysms plus 1 or more of the following: venous loops of 31 μm or larger, questionable soft exudate, intraretinal microvascular abnormalities or venous beading, and retinal hemorrhage; (4) level 37: microaneurysms plus hard exudate and/or soft exudate; (5) level 43; microaneurysms plus 1 or more of the following: retinal hemorrhages/microaneurysms greater than or equal to standard photograph 1 in 4 to 5 fields, retinal hemorrhages/microaneurysms greater than or equal to standard photograph 2A in 1 field, intraretinal microvascular abnormalities in 1 to 3 fields; (6) level 47: microaneurysms and retinal hemorrhages/microaneurysms characteristics from level 43, intraretinal microvascular abnormalities in 4 to 5 fields, retinal hemorrhages/microaneurysms greater than or equal to standard photograph 2A in 2 to 3 fields, and venous beading in 1 field; (7) level 53: microaneurysms plus 1 or more of the following: any 2 or 3 of level 47 characteristics, retinal hemorrhages/microaneurysms greater than or equal to standard photograph 2A in 4 to 5 fields, intraretinal microvascular abnormalities greater than or equal to standard photograph 8A, and venous beading in 2 or more fields; (8) level 60 and higher: any of several levels of severity of proliferative retinopathy, including eyes with neovascularization, fibrous proliferations, vitreous hemorrhages and preretinal hemorrhage, scars of scatter panretinal photocoagulation and/or retinopathy ungradable because of vitreous hemorrhage obscuring the retina, phthisis bulbi, or enucleation secondary to a complication of diabetic retinopathy.

In the analyses, eyes that could not be graded for retinopathy because of opacities in the media or enucleation not related to diabetic retinopathy were defined as “cannot grade.” For purposes of classification, if the retinopathy severity could not be graded in an eye, it was considered to have a score equivalent to that in the other eye. Individuals in whom retinopathy severity could not be graded in either eye (n=3) were excluded from the analyses.

Levels of retinopathy for a participant were derived by combining the severity levels for each eye but giving greater weight to the eye with the higher level. In this scheme, participants in a given level were divided into 2 groups: those with the same level in each eye and those with a lesser level in 1 eye. For example, a participant with level 31 retinopathy in each eye is classified by the notation “level 31/31,” whereas a subject with level 31 in 1 eye and either 10 or 21 in the other is classified as “level 31/<31.” This procedure results in a 13-step scale (10/10, 21/<21, 21/21, 31/<31, 31/31, 37/<37, 37/37, 43/<43, 43/43, 47/<47, 47/47, 53/<53, 53/53, ≥60/<60, and ≥60/≥60). One-step or more progression for a person was defined as an increase in 1 level or more (eg, from 10/10 to 21/<21 or greater, or from 31/<31 to 31/31 or greater). Two-steps or more progression for a person was defined as an increase in 2 levels or more (eg, from 10/10 to 21/21 or greater, or from 31/<31 to 37/<37 or greater). Three-steps or more progression for a person was defined as an increase in 3 steps or more (eg, from 10/10 to 31/<31 or greater, or from 31/<31 to 37/37 or greater). Incidence of PDR was estimated from all persons who were free of this complication at the baseline and 4-year follow-up examinations.

Macular edema was defined as thickening of the retina, with or without partial loss of transparency, within 1 disc diameter (about 1.5 mm) from the center of the macula. Clinically significant macular edema was defined as the presence of any one of the following: (1) thickening of the retina within 500 μm of the center of the macula; (2) hard exudates with thickening of the adjacent retina within 500 μm of the center of the macula; or (3) retinal thickening 1 disc area or larger in size, some of which was located within 1 disc diameter of the center of the macula. The incidence of CSME was estimated from data for all persons who had no macular edema and had not been treated with photocoagulation at the baseline or 4-year follow-up examinations. For the purposes of this study, only participants with retinopathy severity level 43 or less in each eye at baseline were included. Of the 1862 subjects who participated in the baseline and 4-year examinations, and who had gradable retinopathy at both examinations, 336 had retinopathy greater than 43/43 at baseline. The current age was defined as the age at the time of the baseline examination. Duration of diabetes was the time interval between diagnosis of diabetes and the baseline examination.

SAS was used for tabulating the data and for developing logistic regression models. Estimates of relative risks across strata were obtained using methods described by Mantel. Sample size estimates were obtained using methods described by Mantel. Sample size estimates were obtained using methods described by Mantel.
Of the 1526 persons who had retinopathy severity at level 43 or less in both eyes at baseline, and who had gradable fundus photographs at both baseline and the 4-year follow-up visit, 1075 participated in the 10-year follow-up and had gradable fundus photographs. Fifty subjects who had developed PDR and 31 subjects who had developed CSME by the 4-year follow-up visit were excluded from the analysis. Inclusion of these subjects in a separate analysis yielded similar results (data not shown). Participants with gradable retinopathy at the 10-year follow-up were younger, had shorter duration of diabetes, had higher glycosylated hemoglobin levels, had lower systolic blood pressure, had lower body mass, had less proteinuria at baseline, and were more likely to be in the younger-onset group than people who did not participate at the 10-year follow-up (Table 1).

The relationship between steps of progression of retinopathy over the first 4 years of the study and subsequent incidence of PDR and CSME by the time of the 10-year follow-up is presented in Table 2. Persons with 1 or more steps of progression of retinopathy over the first 4 years of the study were 5.8 times as likely to develop PDR and 3.8 times as likely to develop CSME over the subsequent 6 years of follow-up as those with no progression of retinopathy. This relationship was independent of retinopathy severity level (Table 3), glycosylated hemoglobin level (Table 4), duration of diabetes (Figures 1 and 2), or type of diabetes (data not shown).

To evaluate whether the relationship between 1 or more (or \( \geq 2 \)) steps of progression and progression to PDR or CSME was reflecting the influence of the “... more than” component, we assessed the significance of only 1 step, of only 2 steps, of only 3 steps, of only 4 steps, and of only 5 steps of progression between the baseline and 4 years of follow-up on PDR and CSME. Each measure of change was significantly associated with incidence PDR or CSME (Figure 3).

The findings of this study show that as few as 1 or more steps of progression in the modified ETDRS retinopathy severity scale over a 4-year period is meaningful in describing risk of incidence of PDR or CSME over the following 6 years. This finding is independent of the initial level of retinopathy severity, glycemia, blood pressure level, and duration and type of diabetes. This finding is supplementary to and consistent with our previous report, which described a greater likelihood of developing

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**RESULTS**

**COMMENT**

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*RR indicates relative risk; CI, confidence interval; and ellipses, reference group.
a progression of visual loss in those eyes with more severe retinopathy 10 years earlier. 23

In planning clinical trials of new therapeutic interventions for diabetic retinopathy, loss of vision is not usually used as a primary end point as this event is infrequent because photocoagulation is likely to be used to treat macular edema or PDR before the development of loss of vision. Thus, edema involving or threatening the center of the macula and retinopathy at or approaching the high-risk proliferative stage, because of their strong association with visual loss, 21,22 have been accepted as primary end points in clinical trials of treatments designed to slow the progression of diabetic retinopathy. However, these are advanced stages of diabetic retinopathy themselves and to use these end points one would need: a very large number of people with any level of retinopathy evaluated for 4 years (approximate sample size would be 10722 for high-risk PDR as an end point and 11290 for CSME as an end point in persons with younger-onset diabetes and 22384 and 15878, respectively, for those with older-onset diabetes [Table 6]); a smaller number of persons evaluated for a longer period; or a study limited to persons with more advanced retinopathy. As a result, progression of retinopathy by 3 steps or more on the ETDRS scale has been accepted as an end point in clinical trials, but there has been a reluctance to accept progression by fewer steps. This end point also requires relatively large sample sizes to demonstrate a 25% reduction in retinopathy in people with no or mild to moderate nonproliferative retinopathy at baseline (levels 10 to 43 in worse eye) (Table 6). This end point would require 1836 persons with type 1 diabetes and 2088 per-

### Table 3. The Relationship of Step-Change in Retinopathy Severity Between Baseline and 4-Year Follow-up and Progression to Proliferative Retinopathy or Clinically Significant Macular Edema by Retinopathy Severity Level at Baseline*

<table>
<thead>
<tr>
<th>Step-Change in Progression of Retinopathy</th>
<th>Level†</th>
<th>Incidence of Proliferative Diabetic Retinopathy</th>
<th>Incidence of Clinically Significant Macular Edema</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10, No. (%)</td>
<td>21, No. (%)</td>
<td>31, No. (%)</td>
</tr>
<tr>
<td>&lt;1</td>
<td>256 (0.8)</td>
<td>89 (3.4)</td>
<td>27 (3.7)</td>
</tr>
<tr>
<td>≥1</td>
<td>255 (12.5)</td>
<td>156 (28.9)</td>
<td>58 (46.6)</td>
</tr>
<tr>
<td>&lt;2</td>
<td>352 (1.1)</td>
<td>135 (5.2)</td>
<td>35 (8.6)</td>
</tr>
<tr>
<td>≥2</td>
<td>159 (18.9)</td>
<td>110 (34.5)</td>
<td>50 (50.0)</td>
</tr>
<tr>
<td>&lt;3</td>
<td>422 (2.6)</td>
<td>163 (7.4)</td>
<td>50 (20.0)</td>
</tr>
<tr>
<td>≥3</td>
<td>89 (25.8)</td>
<td>82 (40.2)</td>
<td>35 (51.4)</td>
</tr>
</tbody>
</table>

* RR indicates relative risk; CI, confidence interval; and ellipses, reference group.
† Levels of retinopathy defined in the “Patients and Methods” section represent level in worst eye.
‡ The RR was computed across levels of retinopathy severity using a Mantel-Haenszel procedure. 18

### Table 4. The Relationship of Step-Change in Retinopathy Severity Between Baseline and 4-Year Follow-up and Progression to Proliferative Retinopathy or Clinically Significant Macular Edema by Glycosylated Hemoglobin Level*

<table>
<thead>
<tr>
<th>Step-Change in Progression of Retinopathy</th>
<th>Quartile of Glycosylated Hemoglobin, %</th>
<th>RR† (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5.4-8.5, No. (%)</td>
<td>8.6-10.0, No. (%)</td>
</tr>
<tr>
<td>&lt;1</td>
<td>189 (0.5)</td>
<td>121 (3.3)</td>
</tr>
<tr>
<td>≥1</td>
<td>82 (6.1)</td>
<td>127 (12.6)</td>
</tr>
<tr>
<td>&lt;2</td>
<td>231 (0.9)</td>
<td>175 (3.4)</td>
</tr>
<tr>
<td>≥2</td>
<td>40 (10.0)</td>
<td>73 (19.2)</td>
</tr>
<tr>
<td>&lt;3</td>
<td>252 (12.2)</td>
<td>206 (4.9)</td>
</tr>
<tr>
<td>≥3</td>
<td>19 (15.8)</td>
<td>42 (23.8)</td>
</tr>
</tbody>
</table>

* RR indicates relative risk; CI, confidence interval; and ellipses, reference group.
† The RR was computed across levels of glycosylated hemoglobin using a Mantel-Haenszel procedure. 18
sons with type 2 diabetes (assuming \( \alpha = .05 \), \( \beta = .20 \), 2-tailed) to demonstrate a 25% reduction in retinopathy in people with no retinopathy at baseline (level 10 in both eyes). Because of this, clinical trials in which subjects do not have retinopathy in either eye at baseline require a design using another, earlier end point. Data from the current study suggest that both 1-step or more and 2-steps or more progression in retinopathy are possible alternative end points in such trials and would result in a shorter duration of the trial, smaller numbers of subjects needed, or both.

In the context of clinical trials, the Federal Food and Drug Administration defines clinically meaningful end points as ones that measure directly how a patient feels, functions, or survives.\textsuperscript{23} Step progression in the retinopathy severity scale would thus be considered a surrogate end point by this definition. Acceptance of surrogate end points in clinical trials requires that they be reliable, consistent, that they be in the casual pathway, and that changes in the surrogate end point result in changes in clinically important outcomes.\textsuperscript{23} Epidemiological studies, such as the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR),\textsuperscript{4,10-14} and clinical trials, such as the Diabetes Control and Complications Trial\textsuperscript{2,23} and United Kingdom Prospective Diabetes Study,\textsuperscript{6} have provided data demonstrating the validity of step-changes of progression of retinopathy as being valid surrogate end points. For example, in the Diabetes Control and Complications Trial, better glycemic control (with less frequent 3-step progression) found in the intensive insulin group at the end of the clinical trial was associated with lower incidence of PDR and need for laser photocoagulation than in the conventional treatment group, which has poorer glycemic control and a higher frequency of 3-step progression.\textsuperscript{25} In the conventional treatment arm of that study, there were 489 type 1 diabetic subjects who did not develop a sustained 3-step progression of their retinopathy by year 5, of whom 39 (8%) developed severe nonproliferative or PDR 4 to 8 years later compared with 43 (43%) of the 101 who had 3-step or more sustained progression of their retinopathy. In the intensive arm of the study, comparable numbers were 1.8% and 22.2% who developed severe nonproliferative or PDR, respectively (personal communication, Paddy Cleary and Saul Genuith, Diabetes Control and Complications Trial and Epidemiology of Diabetes Interventions and Complications Research Group, May 31, 2000, unpublished data). While data from clinical trials are necessary in demonstrating that changes in the surrogate end point result in changes in clinically important outcomes, few have the length or duration of the WESDR to show that even fewer steps of progression or microaneurysm count changes are strongly associated with the incidence of late clinically meaningful changes, such as PDR or macular edema.

Choice of a specific measure as a primary end point in clinical trials must be made with caution. Using fewer
steps of progression of retinopathy as an end point is associated with increased misclassification related to both biological and grading variability. For example, using the ETDRS severity scale, complete agreement of 2 independent gradings in the ETDRS is 38%, agreement within 1-step is 71%, and agreement within 2 steps is 87%. In the Diabetes Control and Complications Trial, which used 2 independent gradings and adjudication of differences that arose, complete agreement varied from 53.3% to 67.6%, agreement within 1 step varied from 84.3% to 95.0%, and agreement within 2 steps varied from 96.2% to 98.3%. The approach used in the WESDR was similar. The reliability of grading photographs over time to detect change would be expected to be lower.

Other considerations in selecting an end point in a clinical trial are the potential adverse effects of the treatment or drug being tested. A potential limitation of using progression in earlier stages of retinopathy is the resultant smaller sample size and the shorter duration of the trial, permitting too short a time for complications or adverse effects to be manifest. This would result in little insight regarding the longer-term benefits and safety of the treatment or drug, limiting potential cost-effectiveness analyses for comparisons with other treatments or with different drug classes. For example, in a primary prevention trial, one may wish to observe a sizable reduction (more steps) in progression of retinopathy when the treatment is associated with a high rate and severity of adverse effects (eg, severe hypoglycemic reactions as experienced with intensive insulin treatment). The corollary is that to justify the risk of such a severe adverse effect, a large benefit would be needed over a longer period of observation, including phase 4 trials. For clinical trials of treatment interventions of drugs with established minimal adverse effects or toxicity, fewer steps of progression as the primary end point are likely to be more appropriate.

The estimates presented in our tables and figures were based on the WESDR data with examinations at baseline, and the 4- and 10-year follow-up examinations. In a clinical trial, participants would be examined more frequently, perhaps every 6 months to a year. Our relative risks and odds ratios in Tables 2 through 5 are specific to the WESDR schedule of follow-up examinations.
predictive value of a 1-, 2-, or 3-step change in a study with annual photographs might be different from what we demonstrate, perhaps with higher event rates as retinopathy may also regress over time, and persons with more rapid progression would have an event detected sooner.

CONCLUSIONS

These data confirm the strong association of progression retinopathy of 1 step or more or 2 steps or more with the incidence of PDR and CSME. Both 1-step or more or 2-step or more progression are meaningful outcomes in epidemiological studies in people with diabetes, especially in studies in individuals with no or minimal retinopathy. Using these definitions of progression increases the potential efficiency of a trial by using the information gleaned from those who experience meaningful real but less change than has been considered in other trials. However, choice of fewer steps of progression or microaneurysm counts, with fewer numbers of subjects studied over a shorter duration, severely limits the ability to evaluate the toxicity of the drug and its long-term benefits, and a higher risk of variability and chance of error. Careful consideration of different end points for different treatment trials of the same disease is the most appropriate philosophy to adopt rather than choosing uniform end points based on precedent.

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