Methods to Quantify the Relation between Disease Progression in Paired Eyes

Robert J. Glynn and Bernard Rosner

The authors compared, in the context of diabetic retinopathy, alternative methods of quantifying the extent to which disease progression in one eye increases the risk of subsequent progression in the other eye. Data were gathered on 478 US patients with insulin-dependent diabetes mellitus who participated in the 1983-1988 Sorbinil Retinopathy Trial and were followed up for a median of 41 months. During that time, diabetic retinopathy progressed in 93 right eyes and 77 left eyes. Crude incidence rates of progression for right eyes were 7.7 times higher after the left eye had progressed and, for left eyes, were 4.4 times higher after the right eye had progressed. In eye-specific proportional hazards models that adjusted for increasing rates of progression over time and for baseline risk factors, the comparable relative risks associated with progression in the other eye were 2.6 (95% confidence interval (CI): 1.5, 4.7) for right eyes and 1.4 (95% CI: 0.72, 2.9) for left eyes. Two alternative proportional hazards models that included data on both eyes and accounted for their correlation produced estimated relative risks of 1.9 (95% CI: 1.2, 2.9) and 2.7 (95% CI: 1.8, 3.5), respectively. The more complex models for joint survival integrate information on both eyes and provide more stable estimates than do separate analyses of right or left eyes. Am J Epidemiol 2000; 151:965-74.

diabetes mellitus, insulin-dependent; epidemiologic methods; eye diseases; models, statistical; regression analysis; survival analysis

Paired data commonly are found, for example, in studies of eyes, ears, lungs, kidneys, and knees, as well as in twin studies. Studies of disease development or progression in these settings must consider the intercorrelation between paired outcomes. In this paper, we compare alternative analytical strategies when interest focuses on the interrelation between progression in the paired units. We consider the setting of eye disease, although our results are likely to be applicable to other paired data settings.

For many chronic eye diseases, including glaucoma, cataract, and age-related maculopathy, the presence of disease in one eye is strongly associated with disease in the other eye (1-5). Similarly, when a disease progresses in one eye, the other eye is generally considered to be at increased risk of subsequent progression (6-8). This association has important clinical implications for diseases such as diabetic retinopathy, age-related maculopathy, and glaucoma, for which prevention of irreversible visual loss requires detection and prompt treatment. Quantification of the magnitude of increased risk in the contralateral eye can provide prognostic information for patients and can help determine the need for and frequency of follow-up evaluations of this eye. This quantification is of particular importance, because maintenance of good visual function in the second eye is crucial to overall visual efficiency (9).

Often, a first question to consider when designing and analyzing ophthalmologic studies is whether the eye or the person is the appropriate unit of analysis. The primary considerations when answering this question are the scientific goals and the approach that best addresses these goals. Most studies of risk factors for progression of diabetic retinopathy, as for other eye diseases, have considered the person as the unit of analysis (10, 11). One commonly used approach to evaluating such factors as determinants of disease progression is the proportional hazards model, originally proposed by Cox (12). If progression in each eye is considered a separate outcome in this model, then the association between progression in contralateral eyes requires consideration. As is true of other regression
models applied to ophthalmologic data, failure to consider this association can yield incorrect inferences (13). Specifically, \( p \) values can be either over- or underestimated, and confidence intervals can be either too narrow or too wide. Recently developed statistical methods can appropriately account for this association while estimating relative risks in the proportional hazards model. However, the extent to which these approaches provide different or better estimates of risk, compared with approaches that treat the person as the unit of analysis, remains unclear.

When disease progression is being studied and quantification of the association between eyes is of scientific interest, the eye must be the unit of analysis. Only by relating at what time progression occurs in right and left eyes can we learn the strength of their association. Several analytical issues arise when seeking to determine the extent to which disease progression in one eye increases the risk of subsequent progression in the other eye. The association between eyes may be explained, at least in part, by well-known risk factors common to both eyes. For example, both eyes share the increased risk of progression of diabetic retinopathy associated with elevated levels of glycosylated hemoglobin (14, 15). The question of interest here is whether any association between eyes regarding the risk of progression persists after adjustment for such known risk factors. Another concern is that rates of progression may increase with time after baseline evaluation; as patients age, the duration of their diabetes increases, and their level of retinopathy may approach the study endpoint definition. Such an increase can bias a simple comparison of changes in the risk of progression before and after progression in the other eye, because incidence rates early in the study are lower than later rates.

In this paper, we compare alternative approaches to evaluating risk factors for the progression of diabetic retinopathy and to quantifying the association between progression in paired eyes while accounting for potentially confounding variables. Data for this comparison were taken from the Sorbinil Retinopathy Study, a randomized trial of 497 patients with insulin-dependent diabetes mellitus for whom fundus photographs were taken and graded according to protocol over a median follow-up period of 41 months.

**MATERIALS AND METHODS**

**Study population**

Details concerning the subjects and methods of the Sorbinil Retinopathy Trial have been presented previously (16, 17). Briefly, between August 1983 and October 1986, the trial randomized 497 type I (insulin-dependent) diabetic patients at 11 clinical centers in the United States to treatment with sorbinil, an aldose reductase inhibitor, or to placebo. Eligible subjects were aged 18–56 years at entry, had insulin-dependent diabetes mellitus and had begun insulin treatment prior to age 40 years, and had received 1–15 years of insulin treatment. Additionally, patients were required to have a total glycosylated hemoglobin level of more than 9.25 percent (normal range for the study control laboratory, 6.0–8.8 percent) and absent or very mild retinopathy (five or fewer microaneurysms and no other abnormalities in each eye). Female patients were required to be postmenopausal, surgically sterile, or have an intrauterine device in place.

**Measures**

Both the screening and randomization examinations included fundus photographs of each eye. Outcomes were first assessed 12 months after randomization and thereafter at 9-month intervals. Additionally, during the last 4 months of the trial (March–June 1988), all participants were scheduled for a final visit, and extensive efforts were made to encourage all participants, including those who had stopped taking the study medication, to attend.

The Fundus Photograph Reading Center graded the photographs of each eye independently by using the Early Treatment Diabetic Retinopathy Study (ETDRS) adaptation of the modified Airlie House classification (18). The primary endpoint of the trial was worsening of a patient’s severity of retinopathy by two or more steps. To determine this endpoint, the retinopathy levels in the two eyes were combined to obtain an overall level of retinopathy (16, 18), defined by the level in the worse eye and subdivided into two levels according to the one in the contralateral eye (equal vs. less severe). For our analysis, we considered progression in each eye separately, required for evaluation of the association between progression in paired eyes. We defined progression in an eye as an increase of two or more levels from the ETDRS grade of retinopathy in that eye at randomization. For 13 participants, randomization levels of retinopathy were missing, so values from the screening examination were used as baseline levels to evaluate progression.

Other measures potentially related to the progression of retinopathy were assessed at baseline. Included were duration of diabetes (years), glycosylated hemoglobin level (the mean of two values taken at screening and randomization), systolic blood pressure, diastolic blood pressure, and fasting lipid levels, including total, low density lipoprotein, and high density lipoprotein cholesterol (mg/dl). Preliminary analyses indicated that duration of diabetes, glycosylated hemo-
globin level, diastolic blood pressure, and total cholesterol were independent predictors of progression; these measures were maintained, along with randomized treatment assignment, for further evaluation of the association of progression in both eyes. Sixteen randomized subjects had no follow-up evaluations of retinopathy, and, for an additional three subjects, values for these independent variables were missing. Thus, all analyses presented here were based on the 478 subjects who had some follow-up and no missing covariates. To reduce the influence of outlying values on regression analyses, three total cholesterol values of more than 310 mg/dl (>3 standard deviations (SD) from the mean) were recoded to 310 mg/dl and one value of less than 100 mg/dl was recoded to 100 mg/dl.

Analysis

We first obtained rates of progression, separately for right and left eyes, by dividing the number of eyes that progressed from the baseline level by person-years of follow-up. We also determined these rates of progression for each eye (always from the baseline retinopathy level) before and after progression in the other eye. For example, we separately determined rates of progression for right eyes that were followed until either the left eye progressed or follow-up ended and for right eyes that were followed after the left eye progressed. The ratio of these rates, before and after progression in the contralateral eye, provided a first measure of increased risk of progression following progression in the other eye. The p values and confidence intervals for these relative rates were based on the assumption of underlying Poisson distributions (19).

As an alternative simple analysis, we fitted a proportional hazards model with progression in one eye as the dependent variable and progression in the contralateral eye as a time-varying covariate. Specifically, we first fitted a model that predicted progression in the right eye and included progression in the left eye as a time-varying covariate. Specifically, we first fitted a model that predicted progression in the right eye and included progression in the left eye as a time-varying covariate, initially coded as 0 for all participants but then as 1 if the left eye progressed by two or more levels before the right eye did. A parallel model evaluated progression in the right eye as a predictor of progression in the left. We used the PHREG procedure in the SAS statistical package (20) to fit these models. The proportional hazards model compares eyes that progress at a given time after randomization with other eyes that have not progressed at the same time, thus avoiding bias in the crude analyses from the increasing rates of progression expected with increasing time.

We also used proportional hazards models to account for known determinants of progression when the association between progression in paired eyes is examined. We first evaluated progression in right and left eyes separately and treated the status of the contralateral eye as a time-varying covariate. That is, baseline levels of glycated hemoglobin, duration of diabetes, total cholesterol, sorbinil assignment, and diastolic blood pressure were considered independent variables in a proportional hazards model, with progression in the right eye as the dependent variable. This model also included progression in the left eye as a time-varying covariate. A parallel model evaluated these baseline risk factors and progression in the right eye as predictors of progression in the left eye. This approach, also implemented by using the PHREG procedure in the SAS software package, yielded two separate estimates of the relation between progression in paired eyes as well as two estimates of the effects of other risk factors (20).

In a second multivariate analysis, we considered progression in right eyes and in left eyes as separate observations in the same proportional hazards model. For each eye, progression in the other eye was considered a time-varying covariate, and other baseline risk factors were included as additional independent variables. When standard statistical software is used (e.g., the PHREG procedure in SAS), estimates of the relative risks of progression will be unbiased as long as the sample sizes are not too small and the model for each eye is specified correctly (21). However, standard errors, and hence the p values and confidence intervals associated with these estimates, generally will be invalid because of the relationship between progression in paired eyes. To obtain corrected standard errors (called robust standard errors), several authors have proposed approaches based on generalized estimating equations (22–25). We used the Lin approach because the statistical software is readily available and well described (26), and it has been tested on several data sets including those from the Diabetic Retinopathy Study (25). This approach is also available in the SAS (20) and S-Plus (27) statistical packages.

Our third approach was to apply an alternative formulation of the proportional hazards model proposed by Huster et al. (28) for the setting in which each eye can fail at a different time. Their model, which extends an approach for paired survival data presented by Clayton (29) and by Oakes (30), specifies that for each eye, time to progression follows a Weibull survival distribution (a specific type of proportional hazards model). According to their model, the probability that the right eye has not progressed by time \( t_1 \) and the left eye also has not progressed by time \( t_2 \) is

\[
T(t_1, t_2, \alpha, \beta, \theta) = (S(t_1, \alpha, \beta)^{1-\theta} + S(t_2, \alpha, \beta)^{1-\theta} - 1)^{-1/(\theta - 1)}
\]

where \( \theta \) is the parameter that measures the association between eyes, \( S \) is the Weibull survival distribution that...
describes the separate risk of progression in each eye, $\alpha$ is the Weibull scale parameter, and $\beta$ are regression parameters that may be associated either with person- or eye-specific characteristics. Of particular interest here is the association parameter $\theta$, which is interpretable as the risk of progression in one eye if the other eye is known to have progressed at a given time relative to the risk of progression if the other eye has not progressed by this given time. Huster et al. described maximum likelihood estimation of parameters in their model and also illustrated its application with data from the Diabetic Retinopathy Study. We wrote a program in the computer language Fortran to obtain maximum likelihood estimates of parameters in this model applied to the data from the Sorbinil Retinopathy Trial; our Fortran program is available on request.

Because of our particular interest in the association between progression in paired eyes, we included progression in the contralateral eye as an independent variable in our models. To evaluate the effect of including this variable and to make explicit comparisons with a model for progression that treated the person as the unit of analysis, we refitted these proportional hazards models without this variable. We compared these results with estimates obtained from a proportional hazards model that examined baseline risk factors as determinants of progression in a person, defined as the first time that either eye progressed two or more grades on the ETDRS scale. In alternative person-specific analyses, we considered the same baseline risk factors as determinants of a two-step (and alternatively of a three-step) progression on the person-specific retinopathy scale used in the Sorbinil Retinopathy Trial (16). The Appendix contains explicit specifications of our alternative proportional hazards models.

RESULTS

The mean age of the 478 randomized participants in the Sorbinil Retinopathy Trial was 31.6 (SD, 7.4) years; 25 percent were female. The mean baseline level of glycosylated hemoglobin was 11.9 (SD, 2.0) percent, and mean duration of diabetes was 6.8 (SD, 3.5) years. Mean total cholesterol was 189 (SD, 41) mg/dl, and mean supine diastolic blood pressure, including that for nine participants currently taking antihypertensive medications, was 72.8 (SD, 8.6) mmHg.

Levels of retinopathy in right and left eyes, based on the ETDRS scale, at randomization and at final follow-up are displayed in table 1. The 15 right eyes at level 30 (mild nonproliferative diabetic retinopathy) or level 41 (moderate nonproliferative diabetic retinopathy) at randomization, and the 18 left eyes at these levels, had progressed from level 20 or below determined at the screening visit. Agreement between right and left eyes regarding level of retinopathy was strong but far from perfect: 69 percent of participants had identical baseline levels of retinopathy in their right and left eyes.

### TABLE 1. Cross-classification of retinopathy severity levels*,† of diabetic subjects at randomization and at final follow-up, Sorbinil Retinopathy Trial, United States, 1983–1988

<table>
<thead>
<tr>
<th>Level of retinopathy (right eye)</th>
<th>Level of retinopathy (left eye)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>10</td>
<td>289</td>
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<tr>
<td>20</td>
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</tr>
<tr>
<td>41</td>
<td>1</td>
<td>5</td>
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<tr>
<td>45</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>55</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>61</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>279</td>
<td>478</td>
</tr>
</tbody>
</table>

**Randomization**

<table>
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<tr>
<th>10</th>
<th>139</th>
<th>44</th>
<th>3</th>
<th>0</th>
<th>0</th>
<th>0</th>
<th>0</th>
<th>0</th>
<th>186</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>43</td>
<td>105</td>
<td>26</td>
<td>8</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>183</td>
</tr>
<tr>
<td>30</td>
<td>2</td>
<td>29</td>
<td>20</td>
<td>11</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>62</td>
</tr>
<tr>
<td>41</td>
<td>2</td>
<td>7</td>
<td>8</td>
<td>8</td>
<td>6</td>
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<td>31</td>
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<td>45</td>
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<td>2</td>
<td>1</td>
<td>5</td>
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<td>0</td>
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<tr>
<td>55</td>
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<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>61</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>186</td>
<td>187</td>
<td>58</td>
<td>33</td>
<td>12</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>478</td>
</tr>
</tbody>
</table>

* Levels of retinopathy are based on the Early Treatment Diabetic Retinopathy Study scale.
† Equal levels in right and left eyes are shown in bold type.
and Spearman’s rank correlation between levels in eyes was 0.45.

At maximum follow-up (a median of 41 months after randomization), 16 right eyes had progressed to level 45 (moderately severe nonproliferative diabetic retinopathy), level 55 (severe nonproliferative diabetic retinopathy), or level 61 (proliferative retinopathy); 14 left eyes also had progressed to these levels. A total of 277 participants (58 percent) had identical final levels of severity in their right and left eyes. Among the 201 participants with different levels of progression in their right and left eyes, the difference was only one level for 175 (87 percent) of them. Spearman’s rank correlation between levels in eyes was 0.68.

Over the course of the trial, progression of at least two levels at any time occurred in 93 right eyes and 77 left eyes (table 2). Only 40 participants experienced progression in both eyes, while 90 had unilateral progression. Although agreement was far from perfect, the association between progression in paired eyes was strong, with an odds ratio of 7.1. Right eyes were somewhat more likely to progress than left eyes were, but the difference was not significant according to McNemar’s test \( (p = 0.091) \). The odds ratio of progression in right eyes compared with left eyes, conditional on progression in a single eye, was 1.43 (95 percent confidence interval: 0.94, 2.18).

At any given examination, the percentage of eyes that progressed increased over time (table 3). At the 12-month follow-up, 1.6 percent of right eyes and 2.5 percent of left eyes had progressed. These percentages increased steadily to 11.7 and 7.6 percent, respectively, for eyes examined at 48 months.

Eye-specific rates of progression, according to whether the other eye had progressed, are shown in table 4. A total of 76 right eyes progressed at the same time as or before the left eye. An additional 17 right eyes progressed after the left eye did. Rates of progression for right eyes were 7.7 times higher after the left eye had progressed, relative to before \( (p < 0.001) \). Rates of progression for left eyes were 4.4 times higher after progression in the right eye \( (p < 0.001) \). However, crude relative risks of progression are biased because they fail to account for the increase in rates with time. Moreover, these crude rates are calculated under the assumption that all of the progression occurs during the period that follows progression in the first eye, and they disregard subthreshold progression in the second eye that occurs from baseline to progression in the first eye. Proportional hazards models showed that the relative risk of progression for right eyes was 3.7 times higher \( (p < 0.001) \) after progression in the left eye and that the relative risk of progression for left eyes was 2.1 times higher \( (p = 0.036) \) after progression in the right eye.

To adjust for confounding variables, we also used proportional hazards models (table 5). These adjusted relative risks were weaker than those estimated by using the proportional hazards models shown in table 4. Rates of progression for right eyes were 2.63 times higher for persons whose left eyes had progressed, relative to those with no progression in the left eye \( (p = \ldots) \).

<table>
<thead>
<tr>
<th></th>
<th>No. progressed</th>
<th>Person-years</th>
<th>Rate†</th>
<th>Relative risk‡</th>
<th>Proportional hazards§</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Right eyes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At or before progression in left eye</td>
<td>76</td>
<td>1,412.5</td>
<td>5.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>After progression in left eye</td>
<td>17</td>
<td>41.1</td>
<td>41.4</td>
<td></td>
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</tr>
<tr>
<td>Total</td>
<td>93</td>
<td>1,453.5</td>
<td>6.4</td>
<td>7.7</td>
<td>3.7</td>
</tr>
<tr>
<td><strong>Left eyes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At or before progression in right eye</td>
<td>67</td>
<td>1,411.8</td>
<td>4.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>After progression in right eye</td>
<td>10</td>
<td>47.7</td>
<td>21.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>77</td>
<td>1,459.4</td>
<td>5.3</td>
<td>4.4</td>
<td>2.1</td>
</tr>
</tbody>
</table>

* Progression in an eye defined as an increase of two or more levels from the Early Treatment Diabetic Retinopathy Study grade of retinopathy in that eye at randomization.
† Per 100 person-years.
‡ Rate after progression in the other eye divided by the rate at or before progression in the other eye.
§ Relative risk from a proportional hazards model including only progression in the other eye.
¶ 95% confidence interval for the relative risk.

0.001). For left eyes, however, rates of progression were 1.44 times higher for persons whose right eyes had progressed (p = 0.31). This variability in effects might have been due to chance; for example, three other risk factors (duration of diabetes, diastolic blood pressure, and total cholesterol) were found to have significant effects in analyses of one eye but not the other. Only glycated hemoglobin level displayed a strong and consistently significant effect in separate analyses of each eye.

To provide single, unified estimates of the impact of risk factors on progression of retinopathy, we used models that included data on both eyes (table 5). When outcomes for all 956 eyes were included, the rates of progression were 1.88 times higher for one eye after the other eye had progressed. If the correlation between outcomes was ignored, then the 95 percent confidence interval for this estimated effect (1.21, 2.91) was slightly narrower than the one obtained by accounting for this correlation (1.19, 2.96). After adjustment for the correlation between outcomes, the associated p value was 0.007 for the increased risk of progression after progression in the contralateral eye, which was slightly higher than the naive p value of 0.005 obtained before correction but was still highly significant. Other significant predictors of progression were higher level of glycated hemoglobin, longer duration of diabetes, and higher diastolic blood pressure (p < 0.001) for each. The marginal significance of total cholesterol (naive p = 0.06) lessened after adjustment for the correlation between eyes (robust p = 0.08).

Control for specific risk factors substantially affected the estimated association between risk for paired eyes. Specifically, in a proportional hazards model that included data on both eyes but no covariates, rates of progression were 2.86 times higher for one eye after the other eye had progressed. After control for glycated hemoglobin level, this relative rate was reduced to 2.09. Further control for duration of diabetes and diastolic blood pressure reduced the relative rate to 1.95. Addition of cholesterol level and sorbinil treatment assignment yielded the estimated relative rate of 1.88 shown in table 5.

As an alternative approach in which outcomes for all 956 eyes were included, we fitted the proportional hazards version of the Clayton-Oakes model (29, 30) proposed by Huster et al. (28). According to this model, the relative risk of progression for one eye is 2.65 times higher after progression in the other eye (p < 0.001). Estimated effects of other risk factors in this model were quite similar to those obtained from using the estimating equation approach. In particular, glycated hemoglobin level, duration of diabetes, and diastolic blood pressure were strongly associated with increased risk of progression.

We also fitted proportional hazards models that did not include outcome in the contralateral eye as an independent variable and compared these results with models that treated the person, rather than the eye, as the unit of analysis (table 6). Deleting the status of the contralateral eye from the model had little effect on the estimated relative risks associated with the other independent variables and on their significance levels. The person-specific analyses showed comparable effects but slightly higher p values compared with eyespecific analyses that included both eyes. Effects from a model that predicted a three-step progression on the person-specific retinopathy scale (results not shown) were comparable to those with a two-step progression. Overall, inferences about baseline risk factors from the
TABLE 5. Relative risks of progression* of diabetic retinopathy, including the status of the contralateral eye,† Sorbinil Retinopathy Trial, United States, 1983–1988

<table>
<thead>
<tr>
<th>Variable</th>
<th>Right eyes (n = 478)</th>
<th>Left eyes (n = 478)</th>
<th>Estimating equation approach</th>
<th>p value</th>
<th>Clayto-n-Oakes model (29, 30)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycosylated hemoglobin</td>
<td>1.28 (1.16, 1.41)</td>
<td>1.24 (1.12, 1.37)</td>
<td>1.26 (1.17, 1.35)‡</td>
<td>&lt;0.001</td>
<td>1.28 (1.18, 1.36)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(per 1% increase)</td>
<td></td>
<td></td>
<td>(1.16, 1.35)§</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of diabetes (per 2-year increase)</td>
<td>1.27 (1.12, 1.44)</td>
<td>1.07 (0.93, 1.24)</td>
<td>1.17 (1.06, 1.28)‡</td>
<td>0.001</td>
<td>1.18 (1.06, 1.31)</td>
<td>0.002</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>1.10 (0.98, 1.24)</td>
<td>1.21 (1.07, 1.38)</td>
<td>1.17 (1.07, 1.27)‡</td>
<td>0.001</td>
<td>1.19 (1.08, 1.32)</td>
<td>0.001</td>
</tr>
<tr>
<td>(per 5 mmHg increase)</td>
<td></td>
<td></td>
<td>(1.07, 1.27)§</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol (per 20 mg/dl increase)</td>
<td>0.99 (0.89, 1.10)</td>
<td>1.16 (1.05, 1.29)</td>
<td>1.07 (1.00, 1.15)‡</td>
<td>0.076</td>
<td>1.07 (0.98, 1.16)</td>
<td>0.15</td>
</tr>
<tr>
<td>Sorbinil assignment</td>
<td>0.71 (0.47, 1.08)</td>
<td>1.30 (0.83, 2.05)</td>
<td>0.96 (0.71, 1.30)‡</td>
<td>0.81</td>
<td>1.03 (0.73, 1.45)</td>
<td>0.86</td>
</tr>
<tr>
<td>(relative to placebo)</td>
<td></td>
<td></td>
<td>(0.69, 1.33)§</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Progression in contralateral eye</td>
<td>2.63 (1.47, 4.69)</td>
<td>1.44 (0.72, 2.90)</td>
<td>1.88 (1.21, 2.91)‡</td>
<td>0.007</td>
<td>2.65 (1.76, 3.54)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(relative to none)</td>
<td></td>
<td></td>
<td>(1.19, 2.96)§</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Progression in an eye defined as an increase of two or more levels from the Early Treatment Diabetic Retinopathy Study grade of retinopathy in that eye at randomization.
† Relative risks (95% confidence intervals) from alternative proportional hazards model; p values obtained from use of the estimating equation approach and the Clayton-Oakes model.
‡ Naive 95% confidence interval.
§ Robust 95% confidence interval.

DISCUSSION

The simplest approach to evaluating the association between eyes regarding disease progression compares rates of progression for one eye before and after progression in the other eye. Analyses of data from the Sorbinil Retinopathy Trial illustrate two limitations of using this approach. First, overall rates of progression increased over time, which may have artificially increased the relative risk of progression for the second eye, because such progressions tended to occur later in the trial. Moreover, at the time that one eye progressed, the other eye may already have progressed by 1 grade (or perhaps 1.5 grades if retinopathy were measurable on a finer scale). Second, these crude analyses did not account for other known risk factors for progression, for which control in proportional hazards models substantially attenuated the association between progression in paired eyes. Such control is important when evaluating whether progression in one eye provides additional prognostic information about progression in the other eye, independent of what is known from levels of baseline risk factors.

Separate proportional hazards analysis of progression in right and left eyes overcomes these two limitations. Specifically, the proportional hazards model accommodates increases in overall rates of progression as long as relative rates are constant across categories of independent variables in the model. The potential impact of ignoring the effects of time and subthreshold progression is illustrated by the difference between crude estimates and proportional hazards estimates shown in table 4. Additionally, unlike the crude analysis, the proportional hazards analysis evaluates relative risks by comparing eyes that have and have not progressed at the same time after randomization. Another advantage of this approach is its ready implementation with software that has been well documented and tested.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Right eyes (n = 478)</th>
<th>Left eyes (n = 478)</th>
<th>First progression in either eye</th>
<th>Progression on person-specific scale</th>
<th>Estimating equation approach</th>
<th>Clayton-Oakes model (29, 30)</th>
<th>P value</th>
<th>Clay- Oakes model (29, 30)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycosylated hemoglobin (per 1% increase)</td>
<td>1.31 (1.19, 1.44)</td>
<td>1.25 (1.13, 1.38)</td>
<td>1.26 (1.17, 1.37)</td>
<td>1.25 (1.17, 1.33)</td>
<td>1.27 &lt;0.001</td>
<td>1.28 (1.18, 1.38)</td>
<td>0.001</td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>Duration of diabetes (per 2-year increase)</td>
<td>1.25 (1.10, 1.42)</td>
<td>1.08 (0.93, 1.25)</td>
<td>1.17 (1.05, 1.30)</td>
<td>1.13 (1.03, 1.24)</td>
<td>1.17 0.002</td>
<td>1.18 (1.06, 1.31)</td>
<td>0.002</td>
<td></td>
<td>0.002</td>
</tr>
<tr>
<td>Diastolic blood pressure (per 5 mmHg increase)</td>
<td>1.13 (1.01, 1.27)</td>
<td>1.21 (1.07, 1.38)</td>
<td>1.15 (1.04, 1.27)</td>
<td>1.13 (1.04, 1.24)</td>
<td>1.17 0.001</td>
<td>1.19 (1.08, 1.32)</td>
<td>0.001</td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>Total cholesterol (per 20 mg/dl increase)</td>
<td>1.00 (0.91, 1.11)</td>
<td>1.17 (1.06, 1.29)</td>
<td>1.06 (0.97, 1.15)</td>
<td>1.02 (0.95, 1.10)</td>
<td>1.08 0.072</td>
<td>1.07 (0.98, 1.16)</td>
<td>0.15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sorbinil assignment (relative to placebo)</td>
<td>0.73 (0.48, 1.11)</td>
<td>1.29 (0.82, 2.03)</td>
<td>0.98 (0.68, 1.39)</td>
<td>0.97 (0.73, 1.30)</td>
<td>0.96 0.80</td>
<td>1.03 (0.73, 1.45)</td>
<td>0.86</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Progression in an eye defined as an increase of two or more levels from the Early Treatment Diabetic Retinopathy Study grade of retinopathy in that eye at randomization.
† Relative risks (95% confidence intervals) from alternative proportional hazards model; p values obtained from use of the estimating equation approach and the Clayton-Oakes model.
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However, a substantial limitation is that no single estimate of the effect or significance of an association is obtained. The Sorbinil Retinopathy Trial data highlighted this problem because the estimated effects of three risk factors of interest, in addition to the association between eyes, varied substantially and had different characterizations of significance (p < 0.05) between eyes. One alternative is to analyze only right or left eyes (or one randomly chosen eye of each participant), but this approach wastes information and would have failed to identify some significant risk factors found in unified analyses of both eyes.

The estimating equation approach overcomes these limitations by producing a valid proportional hazards analysis that includes information on both eyes; as an additional feature, estimated effects are identical to those obtained if the association between outcomes for eyes is ignored. Thus, information on the two eyes is integrated naturally. In our example, robust standard errors of estimated effects generally (but not always) were slightly larger than estimates that ignored the correlation between outcomes. When applying this approach to data from the Diabetic Retinopathy Study, Lin (26) found robust standard errors to be appreciably smaller than naive standard errors. An important design difference, which affects the way in which robust and naive standard errors differ, is that the Diabetic Retinopathy Study randomized contralateral eyes to different treatments whereas the Sorbinil Retinopathy Trial randomized patients to systemic treatment.

The Clayton-Oakes model (29, 30) also has some attractive features. Because it is fully parametric, it can be used to directly obtain the probability of both eyes being free of progression at any time after randomization and the probability that both eyes have progressed at any specific time. It also treats the association between eyes regarding progression as a parameter of primary interest rather than as a nuisance parameter, as the estimating equation approach of Lin (26) does.

To evaluate the association between paired eyes by using the estimating equation approach, we specifically included the time-varying outcome in the contralateral eye as an independent variable (table 5). The Clayton-Oakes model (29, 30) does not include the status of the contralateral eye as an independent variable, but it simultaneously estimates the association between eyes along with the relations of other independent variables with progression. This difference, together with different ways of measuring association when, at the same visit, both eyes are found to have
progressed, likely accounts for the larger and more significant effect of association between eyes found by using the Clayton-Oakes model. Specifically, with the estimating equation approach, we evaluated the increased risk of progression for one eye strictly after the contralateral eye had progressed; with the Clayton-Oakes model, the association parameter increases if both eyes fail at the same time.

Liang et al. (24) described an alternative estimating equation approach that can be used to obtain an independent estimate of the relation between progression in paired eyes. We used the Lin approach because of its simplicity and accessibility and because it directly combines separate results for right and left eyes. One limitation of the current specification of the Clayton-Oakes model (29, 30) is that the model for progression in each eye follows a Weibull survival distribution, which is one specific form of proportional hazards model and hence is less general than the proportional hazards model with an unspecified underlying hazard. Also, implementation of the Clayton-Oakes model is more complex, and available computer programs are less developed.

In clinical trials of diabetic retinopathy, participants typically are seen at prespecified times after randomization. Thus, the exact times during which progression occurs are unknown. We made the common assumption, used previously by Lin (25) and Huster et al. (28) in their analyses of data from the Diabetic Retinopathy Study, that progression occurred on the date when it was first noted. A current area of statistical research focuses on alternative methods of examining risk factors for progression when progression is known to occur only at some time during an interval (31, 32). However, applicability of these methods to the setting of progression of pairs of eyes is unclear (33, 34). Our knowledge that progression occurred only at some time during an interval may have affected our estimates of the association between progression in eyes. When we evaluated incidence rates and relative risk after progression in the contralateral eye, we did not consider at risk those eyes that progressed during the same interval as the contralateral eye; we were specifically interested in the increase in risk after progression in the contralateral eye. With more detailed information about the time of progression, we might have found that some of these eyes progressed after the contralateral eye did. The likely result would have been to increase the estimates of relative risk after progression in the contralateral eye. However, in actual clinical practice, progression of both eyes at the same time may be more common because patients are seen less frequently than in a randomized trial.

We also compared person-specific survival analyses with analyses that consider separately the outcomes for each eye and account for the association between eyes. Our findings were consistent with comparisons of other types of regression models applied to ophthalmologic data (4, 13). Specifically, the analyses including both eyes produced results similar to those from the person-specific analysis with a slight increase in statistical power. Results from other settings (4, 13) suggest that in analyses including both eyes, power would increase more substantially and interpretability would be enhanced if eye-specific risk factors for progression were evaluated. We initially considered intraocular pressure and ocular perfusion pressure as determinants of progression (35) but excluded them from the results presented here because of their weak associations with progression after control for other baseline risk factors.

In summary, our results demonstrate the importance of control for confounding and increased rates of progression over time when interest focuses on the extent of agreement between progression in paired eyes. The estimating equation approach and the Clayton-Oakes model (29, 30) offer substantial advantages over separate analyses of right and left eyes. These approaches control for confounding variables and for time trends in underlying disease rates, and they also integrate the results of separate analyses of right and left eyes. Each approach has advantages and disadvantages relative to the other, and neither is clearly superior.

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APPENDIX

This Appendix summarizes the alternative proportional hazards models used in this paper. The eye-specific analysis assumes that the hazard of progression for the right eye of a participant at time \( t \) with covariates \( X_r(t) \) is
\[
\lambda_r(t; X_r(t)) = \lambda_0(t) \exp(\beta X_r(t)),
\]
where \( \lambda_0(t) \) is an unspecified underlying baseline hazard in the right eye, and the vector of potentially time-varying covariates \( X_r(t) \) can contain both person- and eye-specific covariates including the progression status of the left eye. The regression parameters \( \beta \) are interpretable as log-relative hazards. The separate analysis of the left eye uses the model
\[
\lambda_l(t; X_l(t)) = \lambda_0(t) \exp(\beta X_l(t)),
\]
where the subscript \( l \) denotes characteristics of the left eye.

The model fitted to data on both eyes by using the estimating equation approach assumes a common hazard for all eyes and takes the form
\[
\lambda(t; X(t)) = \lambda_0(t) \exp(\beta X(t)),
\]
where the vector of covariates again can include the time-varying status of the contralateral eye.

The Clayton-Oakes model (29, 30) of Huster et al. (28) assumes that the probability that the right eye has not progressed by time \( t_1 \) and the left eye has not progressed by time \( t_2 \) is
\[
T(t_1, t_2, \alpha, \beta, \theta) = (S(t_1, \alpha, \beta)^1 - t_1)^{(t_2 - t_1)^{(t_2 - t_1)}} + S(t_2, \alpha, \beta)^1 - t_2)^{(t_2 - t_1)} - 1\]
where \( \theta \) is the parameter that measures the association between eyes, and \( S \) is the Weibull survival distribution
\[
S(t, \alpha, \beta) = \exp(-t^\alpha \exp(\beta X(t))).
\]