# Diabetic Retinopathy, Its Progression, and Incident Cardiovascular Events in the ACCORD Trial

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**OBJECTIVE**—Both the presence of diabetic retinopathy and its severity are significantly associated with future cardiovascular (CV) events. Whether its progression is also linked to incident CV outcomes hasn't been assessed.

**RESEARCH DESIGN AND METHODS**—The relationship between retinopathy, its 4-year progression, and CV outcomes (CV death or nonfatal myocardial infarction or stroke) was analyzed in participants in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial who also participated in the ACCORD Eye Study. Retinopathy was classified as either none, mild, moderate, or severe, and worsening was classified as a <2-step, 2–3-step, or >3-step change (that included incident laser therapy or vitrectomy).

**RESULTS**—Participants ($n$ = 3,433) of mean age 61 years had baseline retinal photographs (seven stereoscopic fields). Compared with no retinopathy, the adjusted HRs (95% CI) for the CV outcome rose from 1.49 (1.12–1.97) for mild retinopathy to 2.35 (1.47–3.76) for severe retinopathy. A subset of 2,856 was evaluated for progression of diabetic retinopathy at 4 years. The hazard of the primary outcome increased by 38% (1.38 [1.10–1.74]) for every category of change in retinopathy severity. Additional adjustment for the baseline and follow-up levels of A1C, systolic blood pressure, and lipids either individually or together rendered the relationships between worsening and CV outcomes nonsignificant.

**CONCLUSIONS**—Both the severity of retinopathy and its progression are determinants of incident CV outcomes. The retina may provide an anatomical index of the effect of metabolic and hemodynamic factors on future CV outcomes.

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Diabetic retinopathy is a cardinal manifestation of diabetes characterized by abnormalities in the retinal vasculature. In addition to being the leading cause of working-age adult-onset blindness in the developed world, several large prospective studies have shown that the presence and severity of diabetic retinopathy are independent determinants of future cardiovascular (CV) events in people with diabetes (1–9). In a recent systematic review of 17 studies comprising 14,896 people with type 2 diabetes (of mean age 58 years and mean follow-up 9 years), people with any retinopathy were more than twice as likely to die or suffer a fatal or nonfatal CV event than people without retinopathy, and a fourfold higher risk was noted for people with advanced retinopathy (10). The same review also included four studies comprising 4,438 people with type 1 diabetes (of mean age 33 years and mean follow-up 12 years) and reported a 3.5- to 4-fold higher risk of death as well as CV events in the presence of any retinopathy and a 7-fold higher risk with advanced retinopathy (10).

Several explanations may account for the relationship between retinopathy and CV outcomes. First, both retinopathy and incident CV outcomes are recognized consequences of diabetes. Their association with each other may therefore be due to their mutual link to diabetes. Second, the degree of retinopathy is progressively related to the degree of several independent determinants of CV outcomes, including hyperglycemia, blood pressure, albuminuria, renal insufficiency, dyslipidemia, and other abnormalities. People with higher levels of these determinants would therefore have both more severe retinopathy and a higher incidence of CV outcomes. Third, the microvascular abnormalities present in the retina may also be occurring in many other vascular beds, and CV outcomes may be due in part to accumulated microvascular abnormalities in the myocardial microcirculation, arterial wall (i.e., vasa vasorum), and elsewhere. If this is true, changes in retinal pathology may closely reflect changes in microvascular pathology in these other vascular beds, and people with the most rapid progression in retinal pathology may be the ones most likely to suffer incident CV outcomes.

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial was a large, randomized, controlled trial of the effects of intensive versus standard degrees of glucose lowering, intensive versus standard degrees of systolic blood pressure (SBP) lowering, and the addition of a fibrate versus placebo to a statin on the 5-year

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incidence of serious CV outcomes in people with type 2 diabetes and other CV risk factors (11). A subset of participants also consented to the ACCORD Eye Study, which assessed the effect of the interventions on retinal pathology at baseline and after 4 years of follow-up. Data from individuals in this subset provide a unique opportunity to confirm the relationship between severity of baseline retinopathy and incident CV outcomes and to determine whether the deterioration of retinopathy with time is also linked to incident CV outcomes.

## RESEARCH DESIGN AND METHODS

The design and main results of the ACCORD trial and the ACCORD Eye Study have been previously reported (12,13). In brief, 10,251 middle-aged and elderly people with type 2 diabetes, A1C levels ≥7.5%, and additional CVD risk factors were randomized to the glucose-lowering trial and either the blood pressure–lowering or fibrate trial. Events were ascertained every 4 months. ACCORD participants who did not have a history of proliferative diabetic retinopathy treated with laser photocoagulation or vitrectomy were eligible to also participate in the ACCORD Eye Study. All Eye Study participants provided written informed consent for both the ACCORD trial and the Eye Study.

The ACCORD trial's primary outcome was a composite comprising the first occurrence of a nonfatal myocardial infarction (MI), nonfatal stroke, or CV death. Secondary outcomes analyzed included total MIs and total strokes (i.e., fatal or nonfatal), CV death, and death from any cause. These study outcomes were all adjudicated by investigators masked to treatment allocation. The mean follow-up period for the primary outcome and mortality was 4.7 and 5.0 years (14), respectively.

The eye assessment consisted of comprehensive standardized eye examinations by a study ophthalmologist or optometrist, and fundus photography comprising seven standard stereoscopic fields obtained at baseline and at 4 years of follow-up. The fundus photographs were centrally graded by individuals masked to treatment allocation according to a modified version of the Early Treatment Diabetic Retinopathy Study (ETDRS) Final Diabetic Retinopathy Severity Scale for Persons, which allows graders to classify retinopathy severity using 18 steps (13). The severity of retinopathy at baseline and follow-up was classified as either no retinopathy, mild nonproliferative diabetic retinopathy (NPDR), moderate NPDR, or severe retinopathy (i.e., severe NPDR, proliferative retinopathy, or incident laser therapy or vitrectomy since baseline). Deterioration in diabetic retinopathy was classified as a <2-step, 2–3-step, or >3-step change using the steps in the ETDRS person scale. Anyone who had laser therapy for proliferative retinopathy or vitrectomy was deemed to have developed the most severe stage of diabetic retinopathy and was grouped with the third category (i.e., >3-step change).

### Statistical analysis

Descriptive statistics (mean and SD or proportion) are presented by level of retinopathy, and Kaplan-Meier curves were used to illustrate the proportions of people who suffered an incident outcome by each of the baseline retinopathy categories. Nominal $P$ values <0.05 were deemed to be statistically significant for all analyses.

Tests for trends were performed with the Cochran-Armitage trend test by category of retinopathy for categorical variables (i.e., sex and outcomes) and with simple linear regression for continuous variables (i.e., age, A1C, SBP, and LDL), treating the retinopathy category as a continuous predictor. Cox proportional hazards regression was used to examine the effect of retinopathy category on the ACCORD primary outcome as well as total MI and total stroke. Also included in these models as independent variables were a history of a CV event prior to randomization and design factors, including participation in either the blood pressure or lipid trial, the ACCORD clinical center network in which the participant was recruited, allocation to the intensive glycemia group, allocation to the intensive blood pressure group, and allocation to fibrate. Likelihood-ratio tests comparing models with and without baseline retinopathy were used to test the significance of retinopathy as an independent predictor of outcomes.

Similar analyses of the effect of change in retinopathy on outcomes included fewer people, as only participants with both baseline and follow-up photographs could be analyzed. As follow-up, retinal photographs were only taken at 4 years, and as there was no reason to believe that a stroke or MI would alter the retinal pathology, these analyses included all of the identified CV outcomes regardless of whether they occurred before or after the 4-year fundus photograph. Change in retinopathy with time was assessed by classifying follow-up photographs according to the change from baseline (<2-step, 2–3-step, or >3-step change). It was also assessed by analyzing the stage of retinopathy at follow-up after adjustment for the stage of retinopathy at baseline. The increase in hazard for every category change in retinopathy was determined from models that included the category as a continuous variable.

To explore whether a significant relationship between deterioration of retinopathy during follow-up and outcomes might be explained by changes in levels of A1C, SBP, HDL, LDL, and triglycerides during follow-up, the mean of all levels measured between baseline and the follow-up eye photograph and the baseline levels (i.e., to adjust the follow-up levels for baseline levels) were added to the regression analyses and the likelihood ratio tests were recalculated. If the addition of the baseline and mean follow-up value of all five measurements increased the likelihood ratio $P$ value from <0.05 to ≥0.05, each pair of measurements (i.e., baseline and mean follow-up) was added one at a time to identify which (if any) of the adjusted follow-up levels accounted for the change from nominal significance to nonsignificance.

## RESULTS

Of the 3,472 people recruited for the ACCORD Eye Study, an adequate baseline eye examination was available for 3,433 participants (of mean age 61 years) and for a subset of 2,856 participants in whom progression of retinopathy was evaluated after 4 years of follow-up. Reasons for a missing follow-up eye exam in the 3,472 recruited participants included death ($n$ = 113) and refusal ($n$ = 503). As noted in Supplementary Table 1 and Fig. 1, individuals with progressively greater severity of retinopathy at baseline had higher baseline A1C and SBP levels ($P$ for trend <0.0001) and were more likely to experience the ACCORD primary outcome, an MI, or a stroke ($P < 0.001$). These relationships persisted after adjusting for previous CV disease and the design factors listed above ($P < 0.01$). Thus, as noted in Supplementary Table 1, the adjusted HRs (95% CI) for the primary outcome for mild NPDR, moderate NPDR, severe NPDR, and severe retinopathy compared with people with no retinopathy at baseline were 1.49 (1.12–1.97), 2.18 (1.42–3.37), and 2.35 (1.47–3.76).

As noted in Table 1, individuals with worsening of retinopathy over 4 years had progressively higher A1C levels, SBP, and LDL cholesterol levels at baseline ($P <$ 0.01). Those with greater worsening

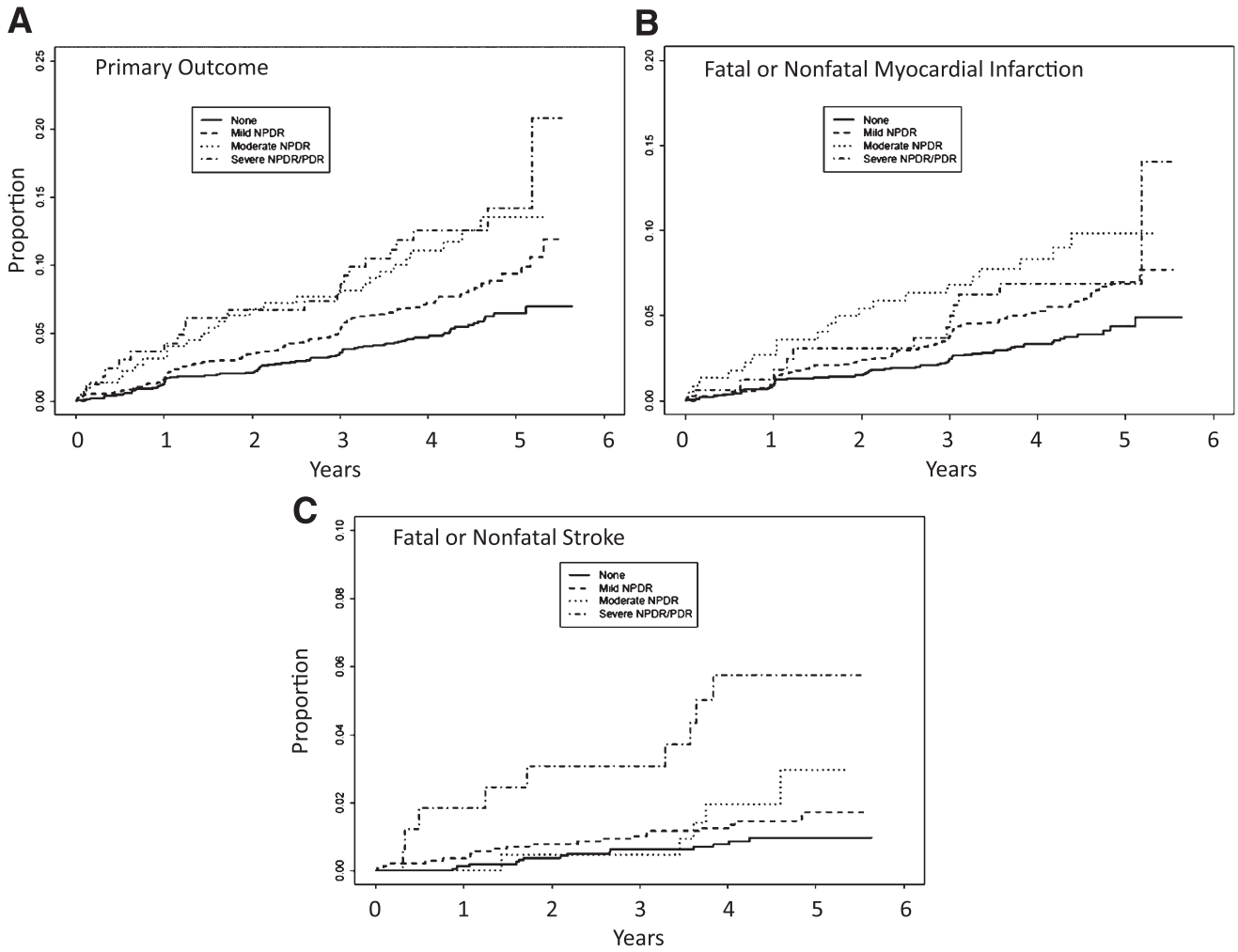


**Figure 1**—*The proportion of participants developing the primary outcome of nonfatal MI, nonfatal stroke, or CV death* (A)*; fatal or nonfatal MI* (B)*; and fatal or nonfatal stroke* (C) *during follow-up according to baseline severity of retinopathy is shown.*

were also more likely to experience the ACCORD primary outcome ($P < 0.001$) and MI ($P = 0.01$). The relationship between change in retinopathy and both the primary outcome and MI was attenuated but remained significant ($P = 0.023$ and $P = 0.049$, respectively) after adjusting for previous CV disease and the design factors listed above. Thus, the hazard of the primary outcome increased by 38% (HR 1.38 [95% CI 1.10–1.74]) for each category of change in the retinopathy severity, and the hazard of MI increased by 40% (1.40 [1.08–1.80]) for every change in category (Table 2 and Fig. 2). A significant relationship between deterioration of retinopathy and the primary outcome was also noted when worsening was assessed by adjusting the severity of retinopathy in the follow-up eye exam for the baseline exam ($P = 0.025$). Using this approach, the hazard of the primary outcome increased by 30% (1.30 [1.04–1.62]) per retinopathy category at follow-up (Supplementary Table 2).

Addition of the mean follow-up A1C, SBP, HDL, LDL, and triglyceride levels to the models and adjustment for baseline levels of these variables rendered the relationships between deterioration of retinopathy over time and both the primary outcome and MI nonsignificant. This was observed for both the model that analyzed change in severity of retinopathy and the model that assessed final severity of retinopathy after adjusting for the baseline severity of retinopathy (data not shown). When the baseline and mean follow-up levels of each of these measures were included separately, each one rendered the likelihood ratio tests nonsignificant (i.e., $P > 0.05$).

**CONCLUSIONS**—These analyses demonstrate a clear relationship between the severity of diabetic retinopathy and the risk of serious CV outcomes in people with type 2 diabetes and additional CV risk factors. Moreover, the rise in adjusted risk from 1.5 in people with mild nonproliferative retinopathy (vs. no retinopathy) to 2.4 in people with severe retinopathy demonstrates that more advanced retinopathy at baseline predicts a higher risk of serious outcomes. These analyses also demonstrate a consistent significant relationship between progression of retinopathy over 4 years and incident CV outcomes such that a greater deterioration of retinal disease over time predicts a higher risk of CV outcomes. Whereas these analyses clearly do not rule out the possibility that the observed relationship may be explained by a variety of measured or unmeasured confounders, the attenuation of the risk relationship after adjustment for baseline and mean follow-up A1C, SBP, and lipids suggests that progression of retinopathy is

**Table 1—*Baseline characteristics, retinopathy progression, and incident ACCORD outcomes**

| Change in retinal pathology | <2 step | 2 or 3 step | >3 step or incident vitrectomy or photocoagulation | *P* for trend |
|---|---|---|---|---|
| *n* | 2,387 | 327 | 142 | |
| Age (years) | 61.6 (6.4) | 61.1 (5.8) | 61.7 (6.9) | 0.54 |
| Females | 906 (38.0) | 129 (39.4) | 55 (38.7) | 0.67 |
| Baseline A1C (%) | 8.2 (1.0) | 8.6 (1.1) | 8.7 (1.2) | <0.0001 |
| Baseline SBP (mm) | 134.0 (16.8) | 136.4 (17.1) | 138.2 (19.4) | 0.0005 |
| Baseline LDL (mg %) | 99.8 (31.8) | 105.2 (37.5) | 104.6 (33.4) | 0.0062 |
| Outcomes during ACCORD | | | | |
| ACCORD primary, *n* (%) | 129 (5.4) | 30 (9.2) | 15 (10.6) | 0.0006 |
| Fatal/nonfatal MI, *n* (%) | 106 (4.4) | 23 (7.0) | 13 (9.2) | 0.0019 |
| Fatal/nonfatal stroke, *n* (%) | 23 (1.0) | 7 (2.1) | 2 (1.4) | 0.15 |

Continuous variables are recorded as means (SD), and counts are *n* (%). *In 2,856 participants in whom progression of retinopathy was evaluated after 4 years of follow-up.

confounded with changes in these levels and CV outcomes. This is consistent with the hypothesis that retinopathy is early anatomic evidence of the effect of changes in these metabolic and hemodynamic risk factors on clinical CV outcomes.

These results suggest that the previously reported relationship between diabetic retinopathy and CV risk in people is also relevant to the people with additional CV risk factors similar to those in the ACCORD trial. The combination of this observation with the novel finding that the relationship is dynamic and that progression of retinopathy is related to a higher CV risk has several implications. It suggests that a similar pathologic process may underlie both diabetic retinopathy and CV disease (15). Thus, CV outcomes may be partially due to pathologic changes in the vasa vasorum of conductance vessels (16,17) or in the myocardial capillaries that are similar to the changes seen in the retina. The related inflammation may promote plaque formation and possibly rupture in these large vessels and/or promote myocardial dysfunction. Alternatively, the retinal microvascular abnormalities may be a consequence of macrovascular disease and reduced vascular flow. The observed link between coronary calcification and retinal abnormalities in people at high risk for CV disease supports both possibilities (6). Our findings also suggest that both processes may be promoted by common underlying metabolic abnormalities that contribute to endothelial dysfunction such as hyperglycemia or dyslipidemia. The current observation that the relationship between change in retinopathy and CV outcomes is rendered nonsignificant after accounting for mean follow-up A1C, SBP, and lipid levels implicates both these abnormalities.

These findings support the view that changes in the retina (which are readily accessible for measurement) may reflect changes in an individual's CV risk and may therefore identify those individuals whose CV risk is rising and who may benefit from particularly aggressive CV risk reduction therapies. Such a possibility could clearly be tested in future clinical trials. Moreover, a retinal benefit of some therapy after only a few years (despite no CV effect during that period) may predict a CV benefit over a much longer period of time. Indeed, the findings of both the Diabetes Control and Complications Trial (in patients with type 1 diabetes) (18,19) and the UK Prospective Diabetes Study (in patients with type 2 diabetes) (20) that therapies that reduce the progression of retinal disease in the short-term subsequently reduce CV outcomes after long-term follow-up support this possibility. If subsequent studies, including ongoing follow-up of the ACCORD participants, support this finding, retinal assessments may become integral to the regulatory assessment of the CV risk of drugs to treat diabetes. Furthermore, whether retinopathy progresses or not could be a gauge of whether a particular patient is reducing his or her risk of CV outcomes in response to the cardioprotective therapies that have been prescribed, and provide an empirical basis to change therapies that are not working.

The strengths of the study include its prospective design, the large number of participants with baseline and follow-up retinal photographs, the standardized central reading of all fundus photographs, and the systematic ascertainment of CV events. However, participants in the Eye Study only had 251 ACCORD primary outcomes, including 174 MIs and 48 strokes during follow-up. Moreover, only 45 primary outcomes, 36 MIs and 9 strokes, occurred in people whose retinal disease progressed, and these were distributed across various degrees of progression. This may have been due to the possibility that the ACCORD participants who volunteered for the eye substudy were likely healthier than the average ACCORD participant. Regardless of the reason, it limited the power of the analysis to reliably detect important effects of various degrees of retinopathy or change in retinopathy on individual CV outcomes. Nevertheless, the clear link

**Table 2—*Hazard ratios (95% CI) of the change in retinal severity vs. <2-step change for each outcome***

| Independent effect of the change in eye | ACCORD primary | Fatal or nonfatal MI | Fatal or nonfatal stroke |
|---|---|---|---|
| <2-step change | 1 | 1 | 1 |
| 2–3-step change | 1.62 (1.08–2.41) | 1.52 (0.97–2.40) | 2.05 (0.88–4.80) |
| >3-step change or incident vitrectomy or photocoagulation | 1.71 (1.00–2.93) | 1.85 (1.03–3.29) | 1.22 (0.29–5.19) |
| *P* (difference across steps) | 0.0227 | 0.0491 | 0.30 |
| HR per category change | 1.38 (1.10–1.74) | 1.40 (1.08–1.80) | 1.34 (0.78–2.30) |

Hazard ratios (compared to <2 step change for each outcome) are estimated from the Cox model adjusted for the clinical center network, CV event prior to randomization (i.e., secondary prevention), blood pressure trial, intensive glycemia group, intensive blood pressure group, and fibrate group; outcomes could have occurred at any time after randomization until the end of ACCORD follow-up.

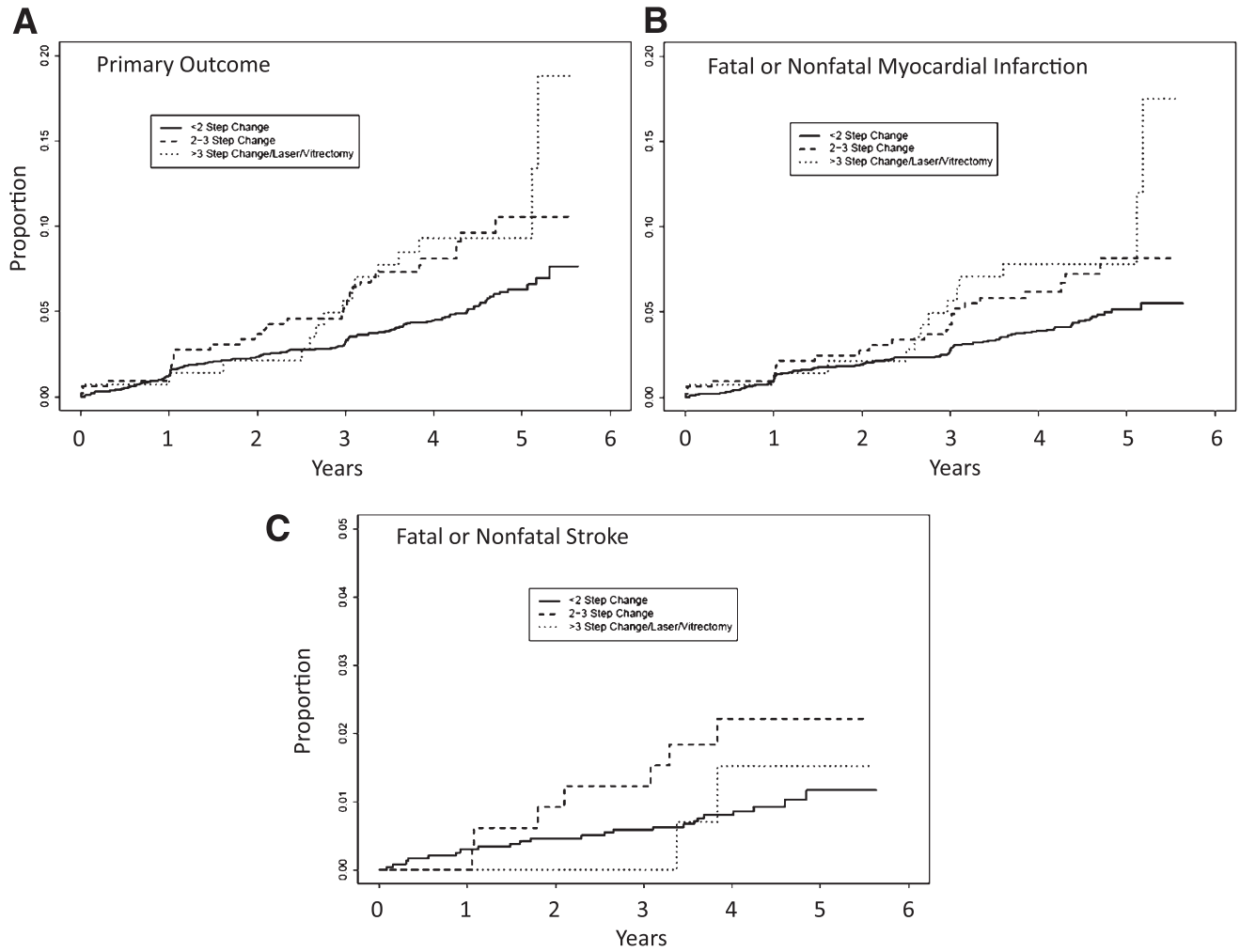


**Figure 2**—*The proportion of participants developing the primary outcome of nonfatal MI, nonfatal stroke, or CV death* (A)*; fatal or nonfatal MI* (B)*; and fatal or nonfatal stroke* (C) *during follow-up according to the change in severity of retinopathy during follow-up is shown.*

between progression of retinal disease and CV disease suggests that these two serious consequences of diabetes may share an underlying pathophysiological basis.

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H.C.G. researched data, wrote the first draft of the manuscript, and discussed, reviewed, and edited the manuscript. W.T.A. researched data, conducted the statistical analyses, and discussed, reviewed, and edited the manuscript. R.D., F.I.-B., W.C., J.C., M.A.B., U.S., and E.Y.C. researched data and discussed, reviewed, and edited the manuscript. H.C.G. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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