Retinal Venular Diameter as an Early Indicator of Progression to Proliferative Diabetic Retinopathy With and Without High-Risk Characteristics in African Americans With Type 1 Diabetes Mellitus

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Objective: To examine the relationship between retinal arteriolar and venular diameter and the 6-year progression of diabetic retinopathy (DR) in African Americans with type 1 insulin-dependent diabetes mellitus.

Methods: Included were 468 African Americans with type 1 diabetes mellitus who participated in the New Jersey 725 and who had undergone a 6-year follow-up examination. Seven standard field retinal photographs were obtained at both examinations. Computer-assisted grading, from digitized images of field 1 of baseline retinal photographs, was accomplished to determine the average diameter of retinal arterioles (central retinal arteriolar equivalent [CRAE]) and venules (central retinal venular equivalent [CRVE]). Retinal vessel diameter was examined in relation to the 6-year incidence and/or progression of DR.

Results: For right and left eyes, mean (SD) CRAE was 168.8 (16.0) µm and mean CRVE was 254.2 (25.2) µm. Both CRAE and CRVE were correlated between eyes (P < .001). Multivariate analysis with generalized estimating equations showed that larger CRVE in either the right or left eye was significantly associated with 6-year progression to either proliferative DR (PDR) or PDR with high-risk characteristics after adjusting for baseline clinical risk factors. Notably, a significant association between baseline CRVE and progression to PDR was present for eyes with no to moderate nonproliferative DR and also between baseline CRVE and progression to PDR with high-risk characteristics for eyes with no or nonproliferative DR.

Conclusion: Larger retinal venular diameter is an independent and early indicator of progression to either PDR or PDR with high-risk characteristics in African Americans with type 1 diabetes mellitus.

tograph Reading Center in Madison, Wisconsin. Detailed clinical information, including sociodemographic and diabetic complications, was obtained, thus providing a unique opportunity to examine whether retinal vessel diameter is a predictor of 6-year progression of DR in this high-risk population.

We hypothesized that larger retinal arteriolar and larger retinal venular diameters, as measured on retinal photographs of field 1 obtained at baseline examination, would predict progression (6-year) of DR in African Americans with type 1 DM.

**METHODS**

**STUDY POPULATION**

The original cohort consisted of 725 African Americans with type 1 DM who participated in the New Jersey 725 study between 1993 and 1998. Patients diagnosed as having DM and treated with insulin before 30 years of age, and currently taking insulin, were identified from a random review of 13,613 medical records. Excluded were patients with type 2 DM, those diagnosed after age 30 years, and patients with maturity-onset diabetes of youth. Of the 875 eligible patients, 725 participated in the baseline examination.

Of the original cohort of 725 patients, 508 (70.1%) participated in the 6-year follow-up examination, 44 (6.1%) could not be located, 34 (4.7%) refused examination, and 139 (19.2%) had died in the 6-year interval. At follow-up, 25 of the 508 participants (4.9%) were no longer receiving insulin and had not received a pancreas transplant. Because these patients may not be truly insulin dependent, they were excluded, as were patients with Buerger disease (n = 1) or systemic lupus (n = 3), not be truly insulin dependent, they were excluded, as were patients with Buerger disease (n = 1) or systemic lupus (n = 3), leaving 479 patients (94.3%) eligible for analysis. Of those eligible, 34 (4.7%) refused examination, and 139 (19.2%) who at baseline had a documented history of CSME. Clinically significant ME (CSME) was defined as thickening of the retina at or within 500 µm of the center of the macula; hard exudates at or within 500 µm of the center of the macula associated with thickening of the adjacent retina; an area of retinal thickening 1 disc diameter or larger, any part of which was within 1 disc diameter or less of the center of the macula; or focal laser photocoagulation scars of the macular area with a documented history of CSME.

Eyes that could not be graded—because of opacities of the media, phthisis, or enucleation—were initially classified as “cannot grade.” For such persons, one of us (M.S.R.) reviewed all previous medical records. When a history of panretinal photocoagulation for PDR or pars plana vitrectomy for complications of PDR was documented by chart review, the DR level was scored as 85. Eyes that had an ETDRS grading less than 61 at the time of examination and had previously received laser photocoagulation for PDR, as documented by chart review, were classified as grade 61.

**PROCEDURES**

Patients were examined in the Eye Clinic at University Hospital in Newark, New Jersey. On arrival, informed written consent was obtained. Patients underwent a complete eye examination including (1) best-corrected visual acuity using the Early Treatment of Diabetic Retinopathy Study (ETDRS) protocol, (2) measurement of intraocular pressure by applanation, (3) dilated retinal examination, and (4) standard stereoscopic Diabetic Retinopathy Study retinal photographs. Also obtained were height and weight. Blood pressure was measured twice in the sitting and standing positions with a random-zero sphygmomanometer according to the Hypertension Detection and Follow-up Program protocol. The average of the 2 measurements in each position was used. A structured clinical interview included detailed medical and ophthalmologic histories, as well as sociodemographic factors and lifestyle variables (ie, self-reported measures of cigarette smoking, alcohol consumption, and illicit drug abuse).

Venous blood was drawn for measurement of total glyco-sylated hemoglobin by means of high-performance liquid chromatography (Bio-Rad; Labcorp Laboratory, Hercules, California) and high- and low-density lipoprotein cholesterol and total cholesterol by means of an enzymatic assay and separation spectrophotometry (Genzyme Diagnostics, Cambridge, Massachusetts). The normal range for total glycosylated hemoglobin is 4.2% to 7.0%, and the intra-assay coefficient of variation, 0.38% to 1.47% (to convert to a proportion of total hemoglobin, multiply by 0.01). A 4-hour timed urine collection was obtained for measurement of albumin excretion rate and creatinuria by spectrophotometry (SmithKline Beecham Clinical Laboratory, Philadelphia, Pennsylvania). The institutional review board of the University of Medicine and Dentistry of New Jersey, New Jersey Medical School, approved the study.

**ASSESSMENT OF RETINAL VESSEL DIAMETERS**

Retinal vessel diameters were measured (at the Ocular Epidemiology Reading Center in Madison) with a computer-assisted technique based on a standard protocol and a modification of formulas established for the Atherosclerosis Risk in Communities Study and described in detail elsewhere. Baseline retinal photographs of field 1 were converted to digital images by means of a high-resolution scanner with identical settings for all photographs. Using a computer software program (Retinal Analysis, Optimate, Madison), trained graders, masked to participant characteristics, measured the diameters of all arterioles and venules coursing through a specified area one-half to 1 disc diameter surrounding the optic disc. On average, 7 to 14 arterioles and an equal number of venules were measured for each eye. Individual arteriolar and venular measurements were combined into summary indexes that reflected the average retinal arteriolar (central retinal arteriolar equivalent [CRAE]) and venular (central retinal venular equivalent [CRVE]) diameter of an eye. The reliability of this retinal vessel grading approach has been shown to be high.

**DEFINITIONS**

The 6-year incidence of any DR was calculated from all patients who at baseline had no DR (severity level 10/10) and who pro-
gressed to a severity level of 20/less than 20 or higher at follow-up. Two-step progression of DR was calculated for all patients who had no DR or nonproliferative DR at baseline (levels 10/10 through 53/53) and progressed at least 2 steps at follow-up (10/10 to 20/20 or higher, or 20/<20 to 35/<35 or higher, etc) as previously described by Klein et al. This scale has 13 steps (10/10, 20/<20, 20/20, 35/<35, 35/35, 43/<43, 43/43, 47/<47, 47/47, 53/<53, 53/53, 61/<61, 61/61+) with all levels of PDR grouped as 1 level. When 2-step progression was examined, patients with PDR at baseline (levels 61/<61 or higher) were excluded. Progression to PDR was calculated for all patients who had no DR or nonproliferative DR at baseline (levels 10/10 through 53/53) and who progressed at follow-up to PDR (levels 61/<61 or worse). Progression to PDR with HRCs was calculated for all patients who had no DR, nonproliferative DR, or PDR without HRCs at baseline (levels 10/10 through 65/65) and who progressed to PDR with HRCs (levels 71/<71 or worse). Progression to vision-threatening DR was calculated for patients who had either no DR or nonproliferative DR at baseline (levels 10/10 through 53/53) or ME and who progressed to either PDR (levels 61/<61 or worse) or ME at follow-up. The 6-year incidence of ME (or CSME) was calculated for all patients who had no ME (or CSME) or had not received focal laser photocoagulation for ME (or CSME) in either eye at baseline and who either developed ME (or CSME) in at least 1 eye at follow-up or had received focal laser photocoagulation for ME in either eye since the baseline examination. When incidence of DR was calculated for individual eyes, similar definitions and data specific for either right or left eyes were used.

Patient’s age was defined as the age at the time of baseline examination. Age at diagnosis of diabetes was the age at which the diagnosis of DM was first recorded by a physician in the patient’s hospital record. Duration of DM was the time between age at diagnosis and age at baseline. Systemic hypertension was defined as present if, at baseline, either the systolic blood pressure was 140 mm Hg or higher or the diastolic blood pressure was 90 mm Hg or higher or if the patient was taking antihypertensive medication. Microproteinuria was defined as present if the baseline albumin excretion rate was 200 µg/min and overt proteinuria if the baseline albumin excretion rate was greater than 200 µg/min. Cardiovascular disease was defined as present if, at baseline, (1) the patient reported having undergone foot or leg amputation for a circulatory problem (excluding amputation secondary to an infection) or having had a myocardial infarction or stroke, and (2) cardiovascular disease was confirmed with standardized criteria by review of the patient’s hospital record. Duration of DM was the time between the diagnosis of DM was first recorded by a physician in the patient’s hospital record. Age at diagnosis of diabetes was the age at which the diagnosis of DM was first recorded by a physician in the patient’s hospital record.

Statistical analyses were performed with SPSS version 17 (SPSS, Inc, Chicago, Illinois). Baseline characteristics of participants and nonparticipants were compared with unpaired, 2-tailed t tests for continuous variables and χ² statistics for categorical variables. Six-year incidence rates with 95% confidence intervals for any DR, 2-step progression of DR, progression to PDR with and without HRCs, progression to vision-threatening DR, and incidence of ME and/or CSME were calculated.

The association of CRAE and CRVE between left and right eyes was assessed with Pearson correlation coefficients. Measures of CRAE and CRVE of right and left eyes were averaged, and the relationship of the mean CRAE and CRVE with baseline clinical characteristics was examined by 1-way analysis of variance. Bivariate associations between CRAE and CRVE and incident outcomes were then assessed with χ² tests. Generalized estimating equations analyses were used to test the association of baseline CRAE and CRVE with incident DR in right and left eyes, adjusting for both systemic and eye-specific predictors. Models were built in 5 successive steps with the following entered in each step: step 1, either CRAE or CRVE; step 2, baseline age, socioeconomic status, and sex; step 3, baseline body mass index, glycosylated hemoglobin level, and proteinuria; step 4, the retinal vessel diameter complementary to that used in step 1; and step 5, ocular perfusion pressure and refractive error. A second model was also built for the same incident outcomes substituting mean arterial blood pressure for proteinuria.

Baseline characteristics of patients are presented in Table 1. Compared with patients who were excluded, those who were included were significantly younger, had lower systolic blood pressure and mean arterial blood pressure, had higher glycosylated hemoglobin values, had higher high-density lipoprotein cholesterol levels, and were less likely to have hypertension, PDR, and/or overt proteinuria.

CRAE AND CRVE IN RIGHT AND LEFT EYES

Mean (SD) CRAE was 168.8 (16.0) µm for both eyes and 168.2 (16.3) µm and 169.9 (17.5) µm for right and left eyes, respectively. Mean CRVE was 254.2 (25.2) µm for both eyes and 254.3 (27.3) µm and 254.6 (27.7) µm for right and left eyes, respectively. Both CRAE and CRVE were significantly correlated between eyes (both r = 0.71, P < .001) and were well approximated by the normal distribution.

RELATIONSHIP BETWEEN MEAN CRAE AND CRVE AND BASELINE CHARACTERISTICS

Mean CRAE was inversely related to age, duration of diabetes, body mass index, mean arterial blood pressure and pulse pressure, severity of DR, ocular perfusion pressure, and myopic refractive error (Table 2). Smaller CRAE was also associated with the presence of hypertension and proteinuria.

Mean CRVE was inversely related to pulse pressure, presence of hypertension, and myopic refractive error (Table 2). Larger CRVE was found in women than in men and in those with more severe DR. Patients who had received laser photocoagulation for PDR had smaller CRAE and CRVE.

RELATIONSHIP BETWEEN CRAE AND CRVE AND 6-YEAR PROGRESSION OF DR

Bivariate Analyses

Table 3 shows that larger CRVE was associated with a higher risk for 6-year progression to both PDR and PDR with HRCs, but neither CRAE nor CRVE was related to any other incident outcomes. Furthermore, there was a suggestion of interaction between baseline DR severity and CRVE. Table 3 shows that progression to PDR or to PDR with HRCs was significantly associated with increasing CRVE for eyes with lower levels of DR severity at baseline (ETDRS level ≤43 for progression to PDR [P = .03] and ETDRS level ≤61 for progression to PDR with HRCs.
For eyes with DR severity higher than these at baseline, however, there was no association between CRVE and progression to PDR or PDR with HRCs.

Multivariate Generalized Estimating Equations Analyses

After adjustment for confounding risk factors including age, sex, socioeconomic status, body mass index, glycosylated hemoglobin value, proteinuria, CRAE, ocular perfusion pressure, and refractive error, increasing baseline CRVE in right and left eyes was associated with at least a tripling of the risk of progression to either PDR or PDR with HRCs (model 1, Table 4). In addition to CRVE, increasing baseline age and glycosylated hemoglobin levels, as well as the presence of proteinuria, were also found to be independently associated with an increased risk of progression to PDR with or without HRCs. When baseline proteinuria was replaced in the model with baseline mean arterial blood pressure, the risk of progression to PDR with or without HRCs was again associated with larger baseline CRVE, increasing age, glycosylated hemoglobin value, and hypertension, the last being significant only for those progressing to PDR (model 2, Table 4). These results were unchanged when generalized estimating equations analyses were repeated for eyes with lower levels of severity of DR at baseline (ETDRS level \(\leq 20\) for PDR and \(\leq 43\) for PDR with HRCs) (data not shown). Thus, the association between CRVE and progression of DR that was apparent at lower levels of DR in Table 3 held up to adjustment.

**COMMENT**

Results of the present study indicate that larger retinal venular diameters, as measured on baseline color reti-
nal photographs by a computer-assisted technique, are indicators of 6-year progression to PDR with or without HRCs in African Americans with type 1 DM, inde-
patients with more severe DR at baseline. In contrast, data from our study suggest that larger CRVE is a more important indicator of progression to PDR with or without HRCs for eyes with less severe DR at baseline (no to moderate nonproliferative DR and no to severe nonproliferative DR, respectively). Thus, larger CRVE appears to be an early indicator of progression to PDR in African Americans with type 1 DM.

The relative dilation of the retinal veins seen in DR and other retinopathies associated with ischemia has been variously interpreted. Wider retinal venules may reflect metabolic changes associated with DM, such as increased lactic acidosis. Stefansson et al also suggested that retinal vessel diameters are influenced by retinal oxygenation and that the dilation of the retinal vasculature may indicate retinal hypoxia. In support of the latter idea is the finding that lower arteriolar oxygen saturation in the blood is associated with larger retinal venular diameters. Another possibility is that dilation of the retinal veins in DR may reflect inflammation, one of the pathogenic factors thought to be involved in the development and/or progression of DR. For instance, wider retinal vessel diameters have been found to be associated with higher levels of inflammatory biomarkers. Wider retinal venules in persons with DM may also reflect endothelial dysfunction. In support of this theory is the fact that the vasodilatory response of the retinal vessels to flicker-light stimulation—which is mediated by nitric oxide—is reduced in persons with DM compared with that of non-diabetic controls and deteriorates further with increasing DR severity. This reduced flicker-induced vasodilation is independent of other risk factors for DM or DR, is more pronounced in patients with type 1 DM, and correlates with retinal vascular caliber measurements.

As previously reported for other populations, there is a high correlation between eyes for both CRAE and CRVE. Myopia and higher ocular perfusion pressure are significantly associated with smaller retinal vessel diameters. However, in the present study, adjusting for refractive error or ocular perfusion pressure did not alter the results.

In our African American patients, panretinal laser photocoagulation is associated with smaller retinal vessel diameters, as previously reported. It has been suggested that laser photocoagulation scars allow more oxygen to reach the inner retina, resulting in retinal arteriolar constriction and reduction in retinal blood flow. This reduction, in turn, may lead to regression of the endothelial cell proliferation and retinal vascular leakage present in DR consistent with the beneficial effects of laser photocoagulation.

Unlike other studies, we found no association between CRAE and any of the incident DR outcomes after adjusting for confounding risk factors. This lack of association may have been due to selective survival in our cohort because retinal arteriolar narrowing is associated with mortality in persons with DM. It is noteworthy that wider retinal arteriolar diameters have been shown to be significantly and independently associated with incidence of DR in persons with type 1 DM and narrower arteriolar diameters with incidence of type 2 DM. Thus, there is increasing evidence from various studies that changes in retinal arteriolar and/or venular...
lar diameters may be clinical predictors of risk for DR as well as for DM.

Strengths of the study include (1) the prospective design with high rates of follow-up for a large cohort of well-characterized African American patients with type 1 DM, (2) use of standardized protocols to document potential confounding variables, (3) masked grading of DR using stereoscopic 7-field retinal photographs, and (4) measurements of the retinal vascular diameters with a previously validated computerized program.

Limitations of the study include the fact that measurement of retinal vessel diameter from color retinal photographs may underestimate the true vascular width because only the red blood cell column is being measured. Conversely, increased retinal pigmentation, as present in African Americans, may lead to an overestimation of the retinal diameter sizes because of reduced contrast between background and retinal vessels.49 Although our results clearly suggest an association between CRVE and progression to either PDR or PDR with HRCs for eyes with less severe baseline DR, a larger sample would be needed to evaluate whether CRVE is a useful indicator in those with more severe baseline DR. Finally, we did not take into account variability of the retinal vessel caliber due to cardiac cycle pulsatility.50

In summary, results of the present study indicate that, in African Americans with type 1 DM, larger CRVE is an independent predictor of progression to PDR with or without HRCs, particularly in eyes with less severe baseline DR, thus providing another early clinical indicator for the progression to the more severe forms of DR. It remains to be seen whether such a measure may be used in the future to monitor treatments for DM and other vascular diseases that specifically target the microvasculature.

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Financial Disclosure: None reported.

### Table 4. Relationship of Baseline CRVE in Right and Left Eyes to 6-Year Progression to Either PDR or PDR With HRCs: Multivariate GEE Analyses

<table>
<thead>
<tr>
<th>Baseline Characteristic</th>
<th>Progression to PDR</th>
<th>P Value</th>
<th>Progression to PDR with HRCs</th>
<th>P Value</th>
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<tbody>
<tr>
<td>No. of eyes at risk (No. progressed)</td>
<td>772 (105)</td>
<td>789 (76)</td>
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<tr>
<td><strong>Model 1</strong></td>
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<tr>
<td>Age (per 10 y)</td>
<td>2.84 (1.77-4.56)</td>
<td>&lt;.001</td>
<td>3.64 (2.12-6.26)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Glycosylated Hb (per 1%)</td>
<td>1.32 (1.22-1.43)</td>
<td>&lt;.001</td>
<td>1.34 (1.20-1.50)</td>
<td>&lt;.001</td>
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<tr>
<td>Proteinuria</td>
<td></td>
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<tr>
<td>Microalbuminuria vs none</td>
<td>2.08 (1.04-4.15)</td>
<td>&lt;.001</td>
<td>4.99 (2.01-12.40)</td>
<td>&lt;.001</td>
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<td>Overt vs none</td>
<td>6.04 (2.72-13.41)</td>
<td>&lt;.001</td>
<td>17.1 (5.96-49.32)</td>
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<tr>
<td>CRVE, µm</td>
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<td></td>
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<tr>
<td>≤235.97</td>
<td>1 [Reference]</td>
<td>1 [Reference]</td>
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<td>235.98-252.89</td>
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<td>1.78 (0.87-3.33)</td>
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<td>252.90-272.26</td>
<td>1.94 (0.84-4.48)</td>
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<td>2.08 (0.72-5.76)</td>
<td>.03</td>
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<td>≥272.27</td>
<td>3.49 (1.44-8.46)</td>
<td>.03</td>
<td>3.61 (1.12-11.57)</td>
<td>.03</td>
</tr>
<tr>
<td>CRAE, µm</td>
<td></td>
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<tr>
<td>≤155.75</td>
<td>1.76 (0.73-4.26)</td>
<td>.60</td>
<td>1.09 (0.36-3.26)</td>
<td>.60</td>
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<tr>
<td>155.76-166.38</td>
<td>1.22 (0.53-2.78)</td>
<td>.60</td>
<td>1.29 (0.44-3.75)</td>
<td>.60</td>
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<tr>
<td>166.39-177.26</td>
<td>1.31 (0.61-2.79)</td>
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<td>1.35 (0.55-3.28)</td>
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<td>≥177.27</td>
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<tr>
<td>No. of eyes at risk (No. progressed)</td>
<td>788 (109)</td>
<td>807 (80)</td>
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<td><strong>Model 2</strong></td>
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<td>Age (per 10 y)</td>
<td>3.07 (1.91-4.92)</td>
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<td>4.11 (2.44-7.03)</td>
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<td>Glycosylated Hb (per 1%)</td>
<td>1.32 (1.22-1.43)</td>
<td>&lt;.001</td>
<td>1.29 (1.18-1.42)</td>
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<td>Mean arterial BP (per 10 mm Hg)</td>
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<td>&lt;.001</td>
<td>1.53 (0.95-2.49)</td>
<td>&lt;.001</td>
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<tr>
<td>CRVE, µm</td>
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<td>235.98-252.89</td>
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<td>2.55 (1.01-6.43)</td>
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<tr>
<td>≥272.27</td>
<td>4.63 (2.02-10.63)</td>
<td>.03</td>
<td>4.62 (1.61-13.29)</td>
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<td>CRAE, µm</td>
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<td>≤155.75</td>
<td>1.99 (0.87-4.55)</td>
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<td>≥177.27</td>
<td>1 [Reference]</td>
<td>1 [Reference]</td>
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Abbreviations: BP, blood pressure; CI, confidence interval; CRAE, central retinal arterial equivalent; CRVE, central retinal venular equivalent; GEE, generalized estimating equation; Hb, hemoglobin; HRCs, high-risk characteristics; OR, odd ratio; PDR, proliferative diabetic retinopathy.

SI conversion factor: To convert glycosylated Hb to a proportion of total Hb, multiply by 0.01.

a Also adjusted for sex, socioeconomic status, body mass index, spherical equivalent, ocular perfusion pressure, and eye.

b Quartiles.

c Adjusted for the same baseline characteristics as in model 1, replacing proteinuria with mean arterial blood pressure.
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REFERENCES