ONLINE FIRST

# Changes in Retinal Vessel Diameter and Incidence and Progression of Diabetic Retinopathy

*Ronald Klein, MD, MPH; Chelsea E. Myers, MStat; Kristine E. Lee, MS; Ronald Gangnon, PhD; Barbara E. K. Klein, MD, MPH*

**Objective:** To describe the relationship of change in retinal vessel diameters to the subsequent 6-year incidence and progression of diabetic retinopathy (DR) and incidence of proliferative diabetic retinopathy (PDR) and macular edema (ME) in persons with diabetes mellitus.

**Design:** A total of 1098 persons with diabetes who had DR graded from fundus photographs and had computer-assisted measurements of the central retinal arteriolar equivalent (CRAE) and central retinal venular equivalent (CRVE) participated in examinations in 1980-1982, 1984-1986, and 1990-1992.

**Results:** During the first 4-year period, the mean change in CRAE and CRVE was −0.37 and 2.54 μm, respectively. The 6-year incidence and progression of DR and the incidence of PDR and ME from 1984-1986 to 1990-1992 were 56%, 39%, 15%, and 11%, respectively. In multivariate analyses, while controlling for duration, diabetes type, and other factors, an increase of 10 μm in CRVE from 1980-1982 to 1984-1986 was associated with increases in the 6-year incidence of DR (odds ratio [OR], 1.26; 95% CI, 1.10-1.43), progression of DR (OR, 1.21; 95% CI, 1.12-1.30), incidence of PDR (OR, 1.19; 95% CI, 1.07-1.32), and incidence of ME (OR, 1.16; 95% CI, 1.03-1.31). No interactions of these associations by diabetes type were found (data not shown). Change in CRAE was unrelated to the incidence or progression of DR (data not shown).

**Conclusions:** Independent of DR severity level, glycemic control, and other factors, widening of the retinal venular but not arteriolar diameter was associated with subsequent incidence and progression of DR. The CRVE may provide additional information regarding the risk of incidence and progression of DR beyond traditional risk factors.

*Arch Ophthalmol. 2012;130(6):749-755.*
*Published online February 13, 2012.*
*doi:10.1001/archophthalmol.2011.2560*

**Author Affiliations:**
Departments of Ophthalmology and Visual Sciences (Drs R. Klein and B. E. K. Klein and Mss Myers and Lee) and Population Health Sciences (Dr Gangnon), University of Wisconsin School of Medicine and Public Health, Madison.

PERSONS WITH DIABETES MELLITUS are at risk of developing diabetic retinopathy (DR) and having it progress to proliferative diabetic retinopathy (PDR) and macular edema (ME) with visual loss.[1] Although traditional risk factors (eg, glycosylated hemoglobin [$HbA_{1c}$] concentration, blood pressure, and duration of diabetes) have been shown to be statistically significantly associated with the incidence and progression of DR, they explain only a limited amount of the risk of developing these complications.[2] Other indicators of increased risk have been suggested, including retinal vessel diameters.[3-5]

Wider retinal venules had been shown in some studies to provide additional information, independent of retinopathy severity, hyperglycemia, hypertension, and other factors, regarding the risk of progression but not incidence of DR.[3,4,6,7] The relationship of retinal arteriolar diameters to the incidence and progression of DR has been less consistent.[3,4,6-8] These observations were usually based on a single measurement of retinal vessel diameter at baseline. In this report, we examine the relationship of change in retinal vessel diameter during a 4-year interval to the incidence and progression of DR in the next 6 years in people with diabetes participating in the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR).

*For editorial comment see page 783*

## METHODS

### STUDY POPULATION

The population, which has been described in previous reports, consisted of a probability sample selected from 10 135 diabetic patients who received primary care in an 11-county area

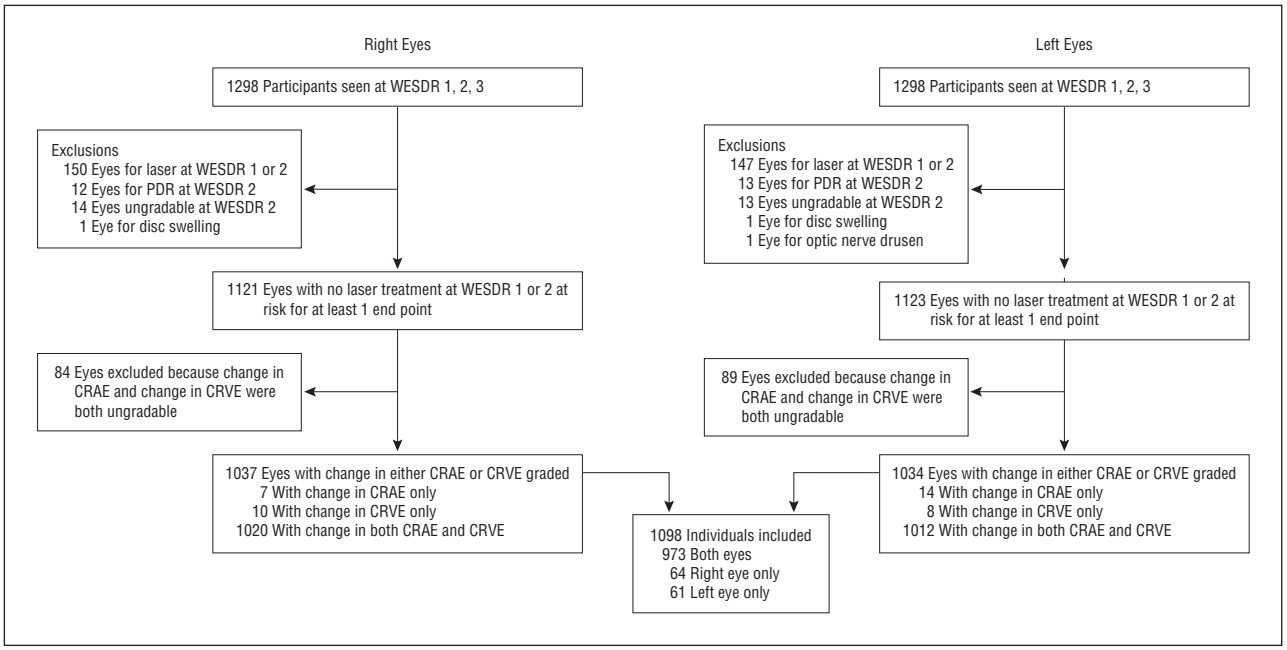


**Figure 1.** Participation and reasons for exclusion in the study. CRAE indicates central retinal arteriolar equivalent; CRVE, central retinal venular equivalent; PDR, proliferative diabetic retinopathy; and WESDR, Wisconsin Epidemiologic Study of Diabetic Retinopathy. 1, 2, and 3 indicate the examination phase number. WESDR 1 is the baseline (1980-1882); WESDR 2, 4-year follow-up (1984-1986); and WESDR 3, 10-year follow-up (1990-1992).

in southern Wisconsin from 1979 to 1980.[9-16] This sample was composed of a younger-onset group with type 1 diabetes (all patients diagnosed as having diabetes before 30 years of age who took insulin, n=1210) and an older-onset group with type 2 diabetes (a sample of persons diagnosed as having diabetes at or after 30 years of age who were treated with diet, oral hypoglycemic agents, and/or insulin, n=1780). Of those selected, 2366 individuals (996 with type 1 diabetes and 1370 with type 2 diabetes) participated in the baseline examination. Data used in the analyses included all participants from both groups (n=1098) who participated in the baseline (1980-1982),[10,11] 4-year follow-up (1984-1986),[12,13] and 10-year follow-up (1990-1992)[14]; had gradable fundus photographs in at least one eye for DR and for measurement of retinal vessel diameter; and did not meet one of the criteria for exclusion involving both eyes (**Figure 1**). Central retinal arteriolar equivalent (CRAE) and central retinal venular equivalent (CRVE) were considered ungradable if one of the largest 6 arterioles or venules, respectively, was not gradable. Reasons for nonparticipation and comparisons between participants and nonparticipants at baseline and all the follow-up examinations have been presented elsewhere.[10-14] The principal reason for nonparticipation was death.

## PROCEDURES

The baseline and follow-up examinations were performed in a mobile examination van in or near the cities where the participants resided. All examinations followed a similar protocol that was approved by the institutional human subjects committee of the University of Wisconsin and that conformed to the tenets of the Declaration of Helsinki. The pertinent parts of the ocular and physical examinations included measuring blood pressure,[17] measuring height and weight, measuring refractive error using the Early Treatment Diabetic Retinopathy Study (ETDRS) protocol, dilating the pupil, determining the presence of cataract using standard lens photographs, taking 30° stereoscopic color fundus photographs of 7 standard fields,[18,19] performing a semiquantitative determination of protein levels in the urine using Labstix (Ames), and determining $HbA_{1c}$ levels from a capillary blood sample.[20] A structured interview was conducted by the examiners, including questions on smoking and specific medications for control of hyperglycemia and blood pressure. If there was any question about medication use or medical history, it was verified by a physician's report.

## GRADING PROTOCOLS

Grading protocols for DR have been described in detail elsewhere[14,21] and are modifications of the ETDRS adaptation of the modified Airlie House classification of DR.[22,23] Interobserver and intraobserver variations and the validity of the systems have been evaluated, and the results have been presented elsewhere.[14,21-23]

## DEFINITIONS

For each eye, the maximum grade in any of the 7 standard photographic fields was determined for each of the lesions and used in defining the retinopathy levels, varying from level 10 (no retinopathy) to level 60 or greater (proliferative retinopathy); definitions have appeared elsewhere.[22,23] The retinopathy level for a participant was derived by concatenating the levels for the 2 eyes, giving the eye with the higher level greater weight. This scheme provided a 15-step DR severity scale.

The incidence of any retinopathy was estimated from all eyes that had no retinopathy at the first follow-up examination (severity level of 10) and were examined again at the following examination. Progression to PDR was estimated from all eyes free of this complication at the second examination. For eyes with no or only nonproliferative retinopathy, progression was defined as the instance of an increase in the severity of retinopathy by 2 steps or more along the 15-step scale from the second to the third examination.

We defined ME as thickening of the retina with or without partial loss of transparency within 1 disc diameter from the center of the macula[24] or the presence of focal photocoagulation scars in the macular area associated with a history of development of ME as documented by stereoscopic fundus photo-

**Table 1. Baseline Characteristics of Individuals Included and Excluded in the Wisconsin Epidemiologic Study of Diabetic Retinopathy (1980-1982)**

| Risk Factor | Included (n = 1098) | | | Excluded (n = 1268) | | | *P* Value[a] |
|---|---|---|---|---|---|---|---|
| | No. | Mean or % | SD | No. | Mean or % | SD | |
| Age, mean, y | 1098 | 40.9 | 20.2 | 1268 | 59.5 | 19.9 | <.001 |
| Sex, % | | | | | | | <.001 |
| Female | 589 | 53.6 | | 629 | 49.6 | | |
| Male | 509 | 46.4 | | 639 | 50.4 | | |
| Body mass index, mean[b] | 1098 | 26.0 | 5.9 | 1258 | 27.0 | 5.5 | <.001 |
| Diabetes duration, mean, y | 1098 | 10.7 | 8.2 | 1268 | 15.1 | 9.8 | <.001 |
| Glycosylated hemoglobin $A_{1c}$, % | 1036 | 9.4 | 2.0 | 1184 | 9.5 | 2.0 | <.001 |
| Systolic blood pressure, mean, mm Hg | 1094 | 128.6 | 20.2 | 1259 | 145.8 | 26.7 | <.001 |
| Diastolic blood pressure, mean, mm Hg | 1092 | 78.5 | 10.7 | 1253 | 79.4 | 12.8 | .007 |
| Hypertension, %[c] | | | | | | | <.001 |
| No | 667 | 61.0 | | 385 | 30.6 | | |
| Yes | 426 | 39.0 | | 875 | 69.4 | | |
| Smoking status, % | | | | | | | .07 |
| Never | 669 | 60.9 | | 691 | 54.5 | | |
| Past | 227 | 20.7 | | 339 | 26.7 | | |
| Current | 202 | 18.4 | | 238 | 18.8 | | |
| Cataract status, right eye, % | | | | | | | <.001 |
| No/questionable | 661 | 62.6 | | 304 | 26.3 | | |
| Less than standard 1 | 368 | 34.8 | | 647 | 56.1 | | |
| Standard 1 or greater | 27 | 2.6 | | 203 | 17.6 | | |
| Refraction, right eye, mean | 1060 | –0.49 | 2.2 | 1026 | 0.2 | 2.3 | .10 |
| Diabetic retinopathy level, % | | | | | | | <.001 |
| None | 495 | 45.1 | | 372 | 29.4 | | |
| Mild | 469 | 42.7 | | 435 | 34.4 | | |
| Moderate | 99 | 9.0 | | 149 | 11.8 | | |
| Proliferative | 35 | 3.2 | | 307 | 24.3 | | |
| Macular edema present, right eye, % | | | | | | | <.001 |
| No | 1038 | 97.5 | | 882 | 86.8 | | |
| Yes | 27 | 2.5 | | 134 | 13.2 | | |
| Poor focus, right eye, % | | | | | | | <.001 |
| No | 1034 | 94.7 | | 973 | 82.0 | | |
| Yes | 58 | 5.3 | | 214 | 18.0 | | |
| Nephropathy present, % | | | | | | | |
| No | 980 | 91.2 | | 864 | 73.5 | | <.001 |
| Yes | 94 | 8.8 | | 312 | 26.5 | | |
| CRAE, right eye, mean, μm | 1098 | 163.0 | 15.1 | 1113 | 154.1 | 17.9 | <.001 |
| CRVE, right eye, mean, μm | 1097 | 243.9 | 23.8 | 1122 | 237.4 | 29.2 | .47 |

Abbreviations: CRAE, central retinal arteriolar equivalent; CRVE, central retinal venular equivalent.
[a] Adjusted for age.
[b] Calculated as weight in kilograms divided by height in meters squared.
[c] Defined as systolic blood pressure of 140 mm Hg or higher and/or diastolic blood pressure of 90 mm Hg or higher and/or use of antihypertensive medication.

graphs. The incidence of ME was estimated from data for all eyes that had no ME and had not been treated previously with photocoagulation at the second examination and were examined again at the third examination.

Diameters of retinal vessels were measured after converting the photographs of field 1 to digital images. All retinal arterioles and venules were measured in the area between half and 1 disc diameter from the optic disc margin using a computer-assisted program. Computer-assisted measurements of individual arterioles and venules were each combined according to formulas developed by Parr and Spears[25] and modified by Hubbard et al[26] and Knudtson et al[27] as mean diameters of the 6 largest retinal arterioles (CRAE) and venules (CRVE) in that eye. Intraclass correlation coefficients were extremely high (>0.90) for both intergrader and intragrader comparisons for both arteriolar and venular measurements (data not shown). Individuals treated with photocoagulation or that had retinal vein or arterial occlusion or other nondiabetic ocular disease affecting the retinal blood vessels were excluded (n=200).

## DEFINITION OF RELATED FACTORS

Age was defined as the age at the time of the baseline examination in 1980-1982. Age at diagnosis of diabetes was defined as the age at the time the diagnosis was first recorded by a physician in the patient's medical record or in a hospital record. The duration of diabetes was defined as the period between the age at diagnosis and the age at the baseline examination.

The means of both systolic and diastolic blood pressures were the means of the last 2 of 3 measurements obtained according to the protocol of the Hypertension Detection and Follow-up Program.[17] Hypertension was defined as a mean systolic blood pressure of 140 mm Hg or higher and/or a mean diastolic blood pressure of 90 mm Hg or higher and/or a history of taking antihypertensive medication at the time of examination. Mean arterial blood pressure (MABP) was defined as (systolic blood pressure + [2 × diastolic blood pressure]) ÷ 3. Body mass index was defined as weight in kilograms divided by the square of height in meters. Proteinuria was defined as a urine protein concentration of 0.03 g/dL or greater (to convert to grams per liter, multiply by 10).

Smokers were identified as persons answering yes to having smoked 100 cigarettes or more in their lifetime and further categorized as current smokers if they had not stopped smoking at the current examination. Cataract was classified as none/questionable, less than a photographic standard of 1, a photographic standard of 1 or more, or cataract surgery. Refraction was performed using a modification of the ETDRS protocol and modeled in categories as moderately to highly myopic (<–3 diopters [D]), mildly myopic (–3 to <–1 D), emmetropic (–1 to 1 D), mildly hyperopic (>1 to 3 D), and hyperopic (>3 D). Nephropathy was defined as a history of kidney transplantation, proteinuria, or dialysis.

### STATISTICAL ANALYSIS

The changes in the CRAE and CRVE were computed between the baseline 1980-1982 examination and the 1984-1986 four-year follow-up examination, whereas the 6-year incidence of DR, PDR, and ME and the progression of DR were computed between the 1984-1986 and 1990-1992 examinations. Generalized estimating equation models with independent correlation structure were used to analyze the relationship of changes in CRAE and CRVE to each diabetic outcome using eye-specific data.[28] Univariate analyses examined a 10-μm change in CRAE and CRVE with the 6-year incidence of DR outcomes. Multivariable analyses additionally controlled for sex, diabetes type, and duration, and changes in retinal photograph focus, cataract status, refraction, $HbA_{1c}$ concentration, MABP, diabetic nephropathy status, smoking status, body mass index, and retinopathy severity level (except in analyses for incident DR).

Change in area under the receiver operating characteristic curve (AUC) was used to measure improvement in prediction when change in CRVE was added to the model based on traditional DR risk factors using the method described by DeLong et al[29] using right eyes only. Results were similar for left eyes (data not shown). Integrated discrimination improvement (IDI) was also computed following the method described by Pencina et al.[30]

## RESULTS

Basline characteristics of the cohort are presented in **Table 1**. Persons were excluded if they did not participate in the 1984-1986 and/or 1990-1992 examination (n=1077), had photocoagulation for PDR or ME in both eyes at the 1980-1982 or 1984-1986 examinations (n=121), did not have gradable retinal vessels in at least one eye (n=58), were not at risk for any of the diabetic outcomes in either eye (n=20), or had nondiabetic retinal vascular conditions in both eyes (eg, retinal vein or arterial occlusion) (n=1). Persons included in the study were younger (40.9 vs 59.5 years of age, $P<.001$), had shorter duration of diabetes (10.7 vs 15.1 years, $P<.001$), had lower systolic (128.6 vs 145.8 mm Hg, $P<.001$) and diastolic (78.5 vs 79.4 mm Hg, $P=.007$) blood pressure, and were less likely to have hypertension (39% vs 69%, $P<.001$) and PDR (3% vs 24%, $P<.001$) compared with nonparticipants.

Between 1984-1986 and 1990-1992, the 6-year incidence of DR was 56%, progression of DR was 39%, incidence of PDR was 15%, and the 6-year incidence of ME was 11%. The mean change in CRAE between 1980-1982 and 1990-1994 was –0.37 μm (SD, 11.3 μm; range, –73.0 to 81.4 μm), and the mean change in CRVE was 2.54 μm (SD, 17.3 μm; range, –108.0 to 78.5 μm). Change in CRAE and CRVE between the right and left eyes was correlated (**Figure 2**).

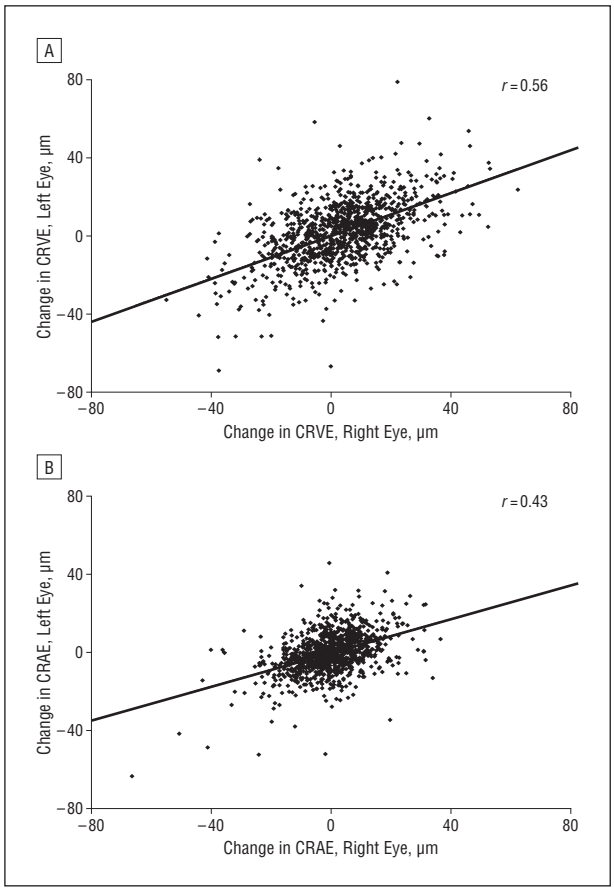


**Figure 2.** Correlation of change between the right and left eyes of participants from baseline to the 4-year follow-up in the Wisconsin Epidemiologic Study of Diabetic Retinopathy. A, Central retinal venular equivalent (CRVE). B, Central retinal arteriolar equivalent (CRAE).

The univariate relationships of 4-year change in CRAE and CRVE to the 6-year cumulative incidence of retinal outcomes are presented in **Table 2**. Increasing CRAE was not associated with any of the DR outcomes, whereas increasing CRVE was associated with increases in all DR outcomes. While controlling for sex, diabetes type, and duration, and change in cataract status, refraction, image focus, $HbA_{1c}$ concentration, MABP, smoking status, diabetic nephropathy, body mass index, and DR level (only in the models of progression of DR and incidence of PDR and ME outcomes), the associations of CRVE but not CRAE remained statistically significant (**Table 3**). These relationships remained when CRAE was added to the CRVE model (data not shown), but an inverse relationship of change in CRAE was found (odds ratio per 10 μm, 0.77; 95% CI, 0.65-0.91; $P=.003$) for the 6-year incidence of PDR when CRVE was added to the CRAE model. No other significant interactions of type or duration of diabetes or MABP with change in CRAE or CRVE were found. When analyses were rerun by type of diabetes, no statistically significant differences were found in any of the relationships of CRAE or CRVE to any of the DR end points (data not shown).

**Table 2. Univariate Relationship of Change in CRAE and CRVE to Incidence and Progression of DR and Incidence of ME and PDR**

| Vessel Measurement | No. at Risk | No. of Events | Odds Ratio (95% CI) | *P* Value |
|---|---|---|---|---|
| Change in CRAE, per 10 μm | | | | |
| Incidence of DR | 663 | 370 | 1.13 (0.97-1.32) | .13 |
| Progression of DR | 1968 | 761 | 1.07 (0.97-1.18) | .15 |
| Incidence of ME | 1885 | 199 | 1.10 (0.96-1.26) | .16 |
| Incidence of PDR | 1968 | 297 | 0.89 (0.78-1.03) | .11 |
| Change in CRVE, per 10 μm | | | | |
| Incidence of DR | 665 | 373 | 1.14 (1.01-1.28) | .03 |
| Progression of DR | 1963 | 761 | 1.13 (1.05-1.22) | <.001 |
| Incidence of ME | 1884 | 197 | 1.20 (1.09-1.32) | <.001 |
| Incidence of PDR | 1963 | 296 | 1.17 (1.05-1.31) | .004 |

Abbreviations: CRAE, central retinal arteriolar equivalent; CRVE, central retinal venular equivalent; DR, diabetic retinopathy; ME, macular edema; PDR, proliferative diabetic retinopathy.

**Table 3. Multivariate Relationships of Change in CRAE and CRVE to Incidence and Progression of DR and Incidence of ME and PDR[a]**

| Vessel Measurement | Odds Ratio (95% CI) | *P* Value |
|---|---|---|
| Change in CRAE, per 10 μm | | |
| Incidence of DR | 1.17 (0.97-1.40) | .10 |
| Progression of DR | 1.11 (0.99-1.24) | .08 |
| Incidence of ME | 1.05 (0.89-1.23) | .56 |
| Incidence of PDR | 0.90 (0.78-1.03) | .13 |
| Change in CRVE, per 10 μm | | |
| Incidence of DR | 1.26 (1.10-1.43) | <.001 |
| Progression of DR | 1.21 (1.12-1.30) | <.001 |
| Incidence of ME | 1.16 (1.03-1.31) | .004 |
| Incidence of PDR | 1.19 (1.07-1.32) | <.001 |

Abbreviations: CRAE, central retinal arteriolar equivalent; CRVE, central retinal venular equivalent; DR, diabetic retinopathy; ME, macular edema; PDR, proliferative diabetic retinopathy.

[a]Controlling for sex, diabetes type, and duration, and change in cataract status, refraction, image focus, glycosylated hemoglobin concentration, mean arterial blood pressure, smoking status, diabetic nephropathy, body mass index, and DR level in the models of progression of DR and incidence of PDR and ME outcomes.

The highest increase and highest incremental gain in the AUC was noted when including change in CRVE in the model that included risk factors for incidence of DR (**Table 4**), which was not statistically significant (*P*=.25). However, analysis using the IDI method showed that adding CRVE significantly increased the predictive ability of the model.

## COMMENT

The data reported herein provide unique, long-term, population-based information regarding the relationship of the change in CRAE and CRVE measurements to the subsequent incidence and progression of DR during 6 years of follow-up in people with diabetes. We found that change in CRVE but not CRAE was statistically significantly associated with the subsequent incidence and progression of DR, independent of other risk factors.

Our finding that increasing CRVE is associated with subsequent higher risk of incident DR may be due to the strong association of wider CRVE with endothelial dysfunction, inflammatory changes, and hyperglycemia, all of which are factors involved in the pathogenesis of DR.[31-34] Our findings are consistent with the results from a small study that examined change in retinal vessel diameter with incidence of DR.[35] In that study involving 45 children with type 1 diabetes, eyes with retinal venular widening greater than 10 μm during the follow-up period were more likely to develop other signs of retinopathy more often than patients with less or no change in the venular diameter. All the other epidemiologic studies[3-8] that have examined these relationships were based on one measurement of retinal vessel diameter before the incidence or progression of DR. Roy et al[7] and others[3,4] showed a direct association of CRVE measured once at baseline with the 6-year incidence of DR in persons with type 1 diabetes, whereas in the WESDR cohort we did not find an association of a single measurement of CRVE at baseline with the 4-year incidence of DR. Others[36] have suggested that widening of retinal arteriolar diameters before the onset of retinopathy would increase the risk of incident retinopathy due to a breakdown in autoregulation. Although Cheung et al[8] found a direct relationship of CRAE with the incidence of DR in persons with type 2 diabetes, we found no association of change (either widening or narrowing) in the arteriolar diameter with the subsequent incidence of DR.

Our findings suggest that change in retinal venular diameter measurements in those without retinopathy may have prognostic value before the development of DR, independent of type or duration of diabetes, glycemic control, blood pressure, and other traditional risk factors. Although the increase in AUC of 2.7% for inclusion of change in CRVE in the model was small and did not reach statistical significance, it compares favorably with other potential predictive factors used for other end points (eg, C-reactive protein and serum high-density lipoprotein cholesterol levels) when added to the Framingham risk score for coronary heart disease in the Atherosclerosis Risk in Communities study.[30,37,38] It was a significant predictor of incidence and progression using an alternative approach, the IDI method, which suggested that adding information from change in CRVE to traditional risk variables (eg, $HbA_{1c}$ concentration) substantially improves the discrimination between those who do and do not develop DR during a 6-year period. There is a need to further study whether measuring change in retinal venular

**Table 4. Change in AUC for Traditional Risk Factor Model Including and Excluding Change in the CRVE**

| Outcome | AUC (95% CI) | | Change in AUC, % | *P* Value[a] | IDI | *P* Value[b] |
|---|---|---|---|---|---|---|
| | Traditional Risk Factor Model Only | Traditional Model and Change in CRVE | | | | |
| Incidence of DR | 0.6879 (0.6241-0.7516) | 0.7067 (0.6450-0.7685) | 2.70 | .25 | 0.0272 | .007 |
| Progression of DR | 0.6547 (0.6167-0.6926) | 0.6698 (0.6323-0.7072) | 2.30 | .12 | 0.0173 | <.001 |
| Incidence of ME | 0.6993 (0.6382-0.7604) | 0.7032 (0.6429-0.7635) | 0.50 | .60 | 0.0060 | .04 |
| Incidence of PDR | 0.7029 (0.6506-0.7552) | 0.7123 (0.6608-0.7638) | 1.30 | .24 | 0.0097 | .03 |

Abbreviations: AUC, area under the receiver operating characteristic curve; CRVE, central retinal venular equivalent; DR, diabetic retinopathy; IDI, integrated discrimination improvement; ME, macular edema; PDR, proliferative diabetic retinopathy.
[a] For difference in AUCs.
[b] For IDI.

diameter is a cost-effective approach to improving prediction of risk resulting in change in management (eg, how often a patient without retinopathy should be seen) and whether such changes ultimately result in further reduction of loss of vision due to these changes.[5,39]

The association in the WESDR of an increase in the venular diameter with progression of DR and incidence of PDR and ME, independent of retinopathy severity, was not unexpected and is consistent with data from earlier studies.[3,4,35,40-46] Increase in venular diameter in eyes with retinopathy is thought to result from retinal hypoxia[47] and from lactate accumulation resulting from hyperglycemia.[48] Retinal venous caliber abnormalities were important predictors of visual loss due to progression of retinopathy in the Diabetic Retinopathy Study.[49] Developers of the classification system at the Airlie House meeting in 1969 were aware of retinal venular widening as a prognostic sign but chose to ignore it in scale "because it was considered too nonspecific and difficult to evaluate."[50(p215)] Retinal venous beading, a more qualitative measure and a sign of irregular venular dilation, was used instead to define the severe nonproliferative retinopathy severity levels of 47 and 53 in the ETDRS severity scale.[24,51] It was significantly associated with progression of proliferative disease in the Diabetic Retinopathy Study and the ETDRS.[23,24]

In the WESDR, the association of change in CRVE to the 6-year progression of DR remained independent of previous change in DR, MABP, diabetic nephropathy, and glycemic control, suggesting that larger venous caliber provides information regarding risk independent of the current ETDRS system used to classify retinopathy severity level. Although the increases in AUC of 2.3% for progression of DR and 1.3% for incidence of PDR were small, the IDI values suggested some value in including these measures for better prognostic assessment beyond measuring only DR severity and other traditional risk factors.

Our study has many strengths. The population is large and involves both types of diabetes, the distribution of severity of retinopathy based on objective recording of DR and ME using stereoscopic fundus photographs of 7 standard fields is broad, and there was a low refusal rate. In addition, standardized protocols of measurement, including computer-assisted measurement of retinal vessel caliber, were consistent over time. However, caution must be exercised in interpreting the findings in the present study. Relationships may have been attenuated by selective survival. Retinopathy severity and retinal arteriolar narrowing and venular widening have been shown to be related to mortality.[52] This finding would reduce the strength of the associations between narrowing of the CRAE and progression of disease and incident PDR and ME.

In summary, measurement of change in CRVE may provide additional information regarding incidence and progression of DR and risk of development of PDR and ME than DR severity by itself in persons with type 1 and type 2 diabetes. The association of change in CRVE with the incidence of DR raises the question of whether measurement of CRVE will provide an even earlier clinically meaningful stage of DR before the onset of microaneurysms and blot hemorrhages.

**Submitted for Publication:** June 28, 2011; final revision received October 21, 2011; accepted November 22, 2011.
**Published Online:** February 13, 2012. doi:10.1001/archophthalmol.2011.2560
**Correspondence:** Ronald Klein, MD, MPH, Department of Ophthalmology and Visual Sciences, University of Wisconsin–Madison, 610 N Walnut St, 417 WARF, Madison, WI 53726-2336 (kleinr@epi.ophth.wisc.edu).
**Financial Disclosure:** None reported.
**Funding/Support:** Funding was provided by research grant EY016379 (Drs R. Klein and B. E. K. Klein) from the National Institutes of Health for the entire study, including collection and analyses of data. Additional funding for data analyses was provided by Senior Scientific Investigator Awards from Research to Prevent Blindness (Drs R. Klein and B. E. K. Klein).
**Disclaimer:** The content of this report is solely the responsibility of the authors and does not necessarily reflect the official views of the National Eye Institute or the National Institutes of Health.
**Additional Contributions:** We are grateful to the participants and the 452 Wisconsin physicians and their staffs who have participated in and supported this study.

## REFERENCES

1. Klein R, Klein BEK. Vision disorders in diabetes. Klein R, Klein BEK, Harris MI, et al, eds. In: *Diabetes in America.* 2nd ed. Bethesda, MD: National Diabetes Data Group, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health; 1995:293-338. NIH publication 95-1468.
2. Klein BE, Klein R, McBride PE, et al. Cardiovascular disease, mortality, and reti-

nal microvascular characteristics in type 1 diabetes: Wisconsin Epidemiologic Study of Diabetic Retinopathy. *Arch Intern Med*. 2004;164(17):1917-1924.
3. Klein R, Klein BE, Moss SE, et al. The relation of retinal vessel caliber to the incidence and progression of diabetic retinopathy, XIX: the Wisconsin Epidemiologic Study of Diabetic Retinopathy. *Arch Ophthalmol*. 2004;122(1):76-83.
4. Klein R, Klein BE, Moss SE, Wong TY. Retinal vessel caliber and microvascular and macrovascular disease in type 2 diabetes, XXI: the Wisconsin Epidemiologic Study of Diabetic Retinopathy. *Ophthalmology*. 2007;114(10):1884-1892.
5. Wong TY. Retinal vessel diameter as a clinical predictor of diabetic retinopathy progression: time to take out the measuring tape. *Arch Ophthalmol*. 2011;129 (1):95-96.
6. Alibrahim E, Donaghue KC, Rogers S, et al. Retinal vascular caliber and risk of retinopathy in young patients with type 1 diabetes. *Ophthalmology*. 2006;113 (9):1499-1503.
7. Roy MS, Klein R, Janal MN. 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. *Arch Ophthalmol*. 2011;129(1):8-15.
8. Cheung N, Rogers SL, Donaghue KC, Jenkins AJ, Tikellis G, Wong TY. Retinal arteriolar dilation predicts retinopathy in adolescents with type 1 diabetes. *Diabetes Care*. 2008;31(9):1842-1846.
9. Klein R, Klein BE, Moss SE, DeMets DL, Kaufman I, Voss PS. Prevalence of diabetes mellitus in southern Wisconsin. *Am J Epidemiol*. 1984;119(1):54-61.
10. Klein R, Klein BE, Moss SE, Davis MD, DeMets DL. The Wisconsin Epidemiologic Study of Diabetic Retinopathy, II: prevalence and risk of diabetic retinopathy when age at diagnosis is less than 30 years. *Arch Ophthalmol*. 1984;102 (4):520-526.
11. Klein R, Klein BE, Moss SE, Davis MD, DeMets DL. The Wisconsin Epidemiologic Study of Diabetic Retinopathy, III: prevalence and risk of diabetic retinopathy when age at diagnosis is 30 or more years. *Arch Ophthalmol*. 1984;102 (4):527-532.
12. Klein R, Klein BE, Moss SE, Davis MD, DeMets DL. The Wisconsin Epidemiologic Study of Diabetic Retinopathy, IX: four-year incidence and progression of diabetic retinopathy when age at diagnosis is less than 30 years. *Arch Ophthalmol*. 1989;107(2):237-243.
13. Klein R, Klein BE, Moss SE, Davis MD, DeMets DL. The Wisconsin Epidemiologic Study of Diabetic Retinopathy, X: four-year incidence and progression of diabetic retinopathy when age at diagnosis is 30 years or more. *Arch Ophthalmol*. 1989;107(2):244-249.
14. Klein R, Klein BE, Moss SE, Cruickshanks KJ. The Wisconsin Epidemiologic Study of Diabetic Retinopathy, XIV: ten-year incidence and progression of diabetic retinopathy. *Arch Ophthalmol*. 1994;112(9):1217-1228.
15. Klein R, Klein BE, Moss SE, Cruickshanks KJ. The Wisconsin Epidemiologic Study of Diabetic Retinopathy, XVII: the 14-year incidence and progression of diabetic retinopathy and associated risk factors in type 1 diabetes. *Ophthalmology*. 1998; 105(10):1801-1815.
16. Klein R, Knudtson MD, Lee KE, Gangnon R, Klein BE. The Wisconsin Epidemiologic Study of Diabetic Retinopathy, XXII: the twenty-five-year progression of retinopathy in persons with type 1 diabetes. *Ophthalmology*. 2008;115(11): 1859-1868.
17. The Hypertension Detection and Follow-up Program Cooperative Group. The hypertension detection and follow-up program: hypertension detection and follow-up program cooperative group. *Prev Med*. 1976;5(2):207-215.
18. ETDRS Research Group. Procedures for completing eye examinations. In: *Early Treatment Diabetic Retinopathy Study (ETDRS) Manual of Operations*. Springfield, VA: National Technical Information Service; 1985:1-74. NTIS Accession No. PB85-223006/AS.
19. ETDRS Research Group. Classification of diabetic retinopathy from stereo color fundus photographs. In: *Early Treatment Diabetic Retinopathy Study (ETDRS) Manual of Operations*. Springfield, VA: National Technical Information Service; 1985:1-54. NTIS Accession No. PB85-223006/AS.
20. Moss SE, Klein R, Klein BE, Spennetta TL, Shrago ES. Methodologic considerations in measuring glycosylated hemoglobin in epidemiologic studies. *J Clin Epidemiol*. 1988;41(7):645-649.
21. Klein R, Klein BE, Magli YL, et al. An alternative method of grading diabetic retinopathy. *Ophthalmology*. 1986;93(9):1183-1187.
22. Early Treatment Diabetic Retinopathy Study Research Group. Grading diabetic retinopathy from stereoscopic color fundus photographs: an extension of the modified Airlie House classification; ETDRS Report Number 10. *Ophthalmology*. 1991;98(5)(suppl):786-806.
23. Early Treatment Diabetic Retinopathy Study Research Group. Fundus photographic risk factors for progression of diabetic retinopathy: ETDRS Report Number 12. *Ophthalmology*. 1991;98(5)(suppl):823-833.
24. ETDRS Research Group. Photocoagulation for diabetic macular edema: Early Treatment Diabetic Retinopathy Study Report Number 1. *Arch Ophthalmol*. 1985; 103(12):1796-1806.
25. Parr JC, Spears GF. General caliber of the retinal arteries expressed as the equivalent width of the central retinal artery. *Am J Ophthalmol*. 1974;77(4):472-477.
26. Hubbard LD, Brothers RJ, King WN, et al. Methods for evaluation of retinal microvascular abnormalities associated with hypertension/sclerosis in the Atherosclerosis Risk in Communities Study. *Ophthalmology*. 1999;106(12):2269-2280.
27. Knudtson MD, Lee KE, Hubbard LD, Wong TY, Klein R, Klein BE. Revised formulas for summarizing retinal vessel diameters. *Curr Eye Res*. 2003;27(3): 143-149.
28. Zeger SL, Liang KY. Longitudinal data analysis for discrete and continuous outcomes. *Biometrics*. 1986;42(1):121-130.
29. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics*. 1988;44(3):837-845.
30. Pencina MJ, D'Agostino RB Sr, D'Agostino RB Jr, Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. *Stat Med*. 2008;27(2):157-172.
31. Tso MO, Abrams GW, Jampol LM. Hypertensive retinopathy, choroidopathy, and optic neuropathy: a clinical and pathophysiological approach to classification. In: Singerman LJ, Jampol LM, eds. *Retinal and Choroidal Manifestations of Systemic Disease*. Baltimore, MD: Williams & Wilkins; 1991:79-127.
32. Klein R, Sharrett AR, Klein BE, et al. Are retinal arteriolar abnormalities related to atherosclerosis? the Atherosclerosis Risk in Communities Study. *Arterioscler Thromb Vasc Biol*. 2000;20(6):1644-1650.
33. Garner A, Ashton N, Tripathi R, Kohner EM, Bulpitt CJ, Dollery CT. Pathogenesis of hypertensive retinopathy: an experimental study in the monkey. *Br J Ophthalmol*. 1975;59(1):3-44.
34. Sharrett AR, Hubbard LD, Cooper LS, et al. Retinal arteriolar diameters and elevated blood pressure: the Atherosclerosis Risk in Communities Study. *Am J Epidemiol*. 1999;150(3):263-270.
35. Falck A, Laatikainen L. Retinal vasodilation and hyperglycaemia in diabetic children and adolescents. *Acta Ophthalmol Scand*. 1995;73(2):119-124.
36. Brinchmann-Hansen O, Heier H, Myhre K. Fundus photography of width and intensity profiles of the blood column and the light reflex in retinal vessels. *Acta Ophthalmol (Copenh)*. 1986;64(S179):9-19.
37. Chambless LE, Folsom AR, Sharrett AR, et al. Coronary heart disease risk prediction in the Atherosclerosis Risk in Communities (ARIC) study. *J Clin Epidemiol*. 2003;56(9):880-890.
38. Folsom AR, Chambless LE, Ballantyne CM, et al. An assessment of incremental coronary risk prediction using C-reactive protein and other novel risk markers: the Atherosclerosis Risk in Communities Study. *Arch Intern Med*. 2006;166 (13):1368-1373.
39. McGeechan K, Macaskill P, Irwig L, Liew G, Wong TY. Assessing new biomarkers and predictive models for use in clinical practice: a clinician's guide. *Arch Intern Med*. 2008;168(21):2304-2310.
40. Practical experience with a method for grading diabetic retinopathy. Oakley NW, Joplin GF, Kohner EM, Fraser TR, Goldberg MF, Fine SL, eds. In: *Symposium on the Treatment of Diabetic Retinopathy*. Washington, DC: US Dept of Health, Education and Welfare; 1968:3-6. Public Health Service publication 1890.
41. Skovborg F, Nielsen AV, Lauritzen E, Hartkopp O. Diameters of the retinal vessels in diabetic and normal subjects. *Diabetes*. 1969;18(5):292-298.
42. Wallace J. Vessel measurements in diabetic fundi. *Proc R Soc Med*. 1970;63(8): 788-791.
43. Stefansson E, Landers MB III, Wolbarsht ML. Oxygenation and vasodilatation in relation to diabetic and other proliferative retinopathies. *Ophthalmic Surg*. 1983; 14(3):209-226.
44. Grunwald JE, Riva CE, Sinclair SH, Brucker AJ, Petrig BL. Laser Doppler velocimetry study of retinal circulation in diabetes mellitus. *Arch Ophthalmol*. 1986; 104(7):991-996.
45. Patel V, Rassam S, Newsom R, Wiek J, Kohner E. Retinal blood flow in diabetic retinopathy. *BMJ*. 1992;305(6855):678-683.
46. Larsen HW. Diabetic retinopathy: an ophthalmoscopic study with a discussion of the morphologic changes and the pathogenetic factors in this disease. *Acta Ophthalmol Suppl*. 1960(suppl 60):1-89.
47. Meehan RT, Taylor GR, Rock P, Mader TH, Hunter N, Cymerman A. An automated method of quantifying retinal vascular responses during exposure to novel environmental conditions. *Ophthalmology*. 1990;97(7):875-881.
48. Keen H, Chlouverakis C. Metabolic factors in diabetic retinopathy. In: Graymore CN, ed. *Biochemistry of the Retina*. New York, NY: Academic Press; 1965:123-131.
49. Rand LI, Prud'homme GJ, Ederer F, Canner PL. Factors influencing the development of visual loss in advanced diabetic retinopathy: Diabetic Retinopathy Study (DRS) Report No. 10. *Invest Ophthalmol Vis Sci*. 1985;26(7):983-991.
50. Diabetic Retinopathy Study Research Group. Report No. 7: a modification of the Airlie House classification of diabetic retinopathy. *Invest Ophthalmol Vis Sci*. 1981; 21(1 pt 2):210-226.
51. The Airlie Classification of Diabetic Retinopathy. Davis MD, Norton EWD, Myers FL, Goldberg MF, Fine SL, eds. In: *Symposium on the Treatment of Diabetic Retinopathy*. Washington, DC: US Dept of Health, Education and Welfare; 1968:7-22. Public Health Service publication 1890.
52. Klein R, Klein BE, Moss SE, Cruickshanks KJ. Association of ocular disease and mortality in a diabetic population. *Arch Ophthalmol*. 1999;117(11):1487-1495.