Retinal Vessel Calibers in Predicting Long-Term Cardiovascular Outcomes

The Atherosclerosis Risk in Communities Study

BACKGROUND: Narrower retinal arterioles and wider retinal venules have been associated with negative cardiovascular outcomes. We investigated whether retinal vessel calibers are associated with cardiovascular outcomes in long-term follow-up and provide incremental value over the 2013 American College of Cardiology/American Heart Association Pooled Cohort Equations in predicting atherosclerotic cardiovascular disease events.

METHODS: A total of 10 470 men and women without prior atherosclerotic cardiovascular disease events or heart failure in the ARIC Study (Atherosclerosis Risk in Communities) underwent retinal photography at visit 3 (1993–1995).

RESULTS: During a mean follow-up of 16 years, there were 1779 incident coronary heart disease events, 548 ischemic strokes, 1395 heart failure events, and 2793 deaths. Rates of all outcomes were higher in those with wider retinal venules and narrower retinal arterioles. Subjects with wider retinal venules (hazard ratio [HR], 1.13; 95% confidence interval [CI], 1.08–1.18; HR, 1.18; 95% CI, 1.07–1.31; and HR, 1.10; 95% CI, 1.00–1.20 per 1-SD increase) and narrower retinal arterioles (HR, 1.06; 95% CI, 1.01–1.11; HR, 1.14; 95% CI, 1.03–1.26; and HR, 1.13; 95% CI, 1.03–1.24 per 1-SD decrease) had a higher risk of death and stroke in both sexes and incident coronary heart disease in women but not men (interaction P=0.02) after adjustment for the Pooled Cohort Equations risk score variables. The association between retinal vessel caliber and heart failure was nonsignificant after adjustment for systolic blood pressure. Among women with Pooled Cohort Equations–predicted 10-year atherosclerotic cardiovascular disease event risk <5% (overall risk, 3.9%), women in the narrowest arteriolar quartile had a 10-year event rate of 5.6% compared with 2.8% for women in the widest quartile (5.0% versus 3.4% for wider versus narrower venules). Retinal vessel caliber reclassified 21% of low-risk women (11% of all women) as intermediate risk (>5%).

CONCLUSIONS: Narrower retinal arterioles and wider retinal venules conferred long-term risk of mortality and ischemic stroke in both sexes and coronary heart disease in women. These measures serve as an inexpensive, reproducible biomarker that added incremental value to current practice guidelines in atherosclerotic cardiovascular disease event risk prediction in low-risk women.

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Clinical Perspective

What Is New?

- The cornea provides a transparent window into the retinal microvasculature that has been related to cardiovascular outcomes.
- Whether retinal vessel caliber can provide incremental value to current practice guidelines (2013 American College of Cardiology/American Heart Association Pooled Cohort Equations) in predicting atherosclerotic cardiovascular disease events has not been established.
- In 10 470 subjects, narrower retinal arterioles and wider retinal venules were associated with long-term risk of mortality and ischemic stroke in both sexes and coronary heart disease in women independently of Pooled Cohort Equations risk score variables.
- Retinal vessel caliber reclassified 21% of low-risk women (11% of all women) as intermediate risk for atherosclerotic cardiovascular disease events.

What Are the Clinical Implications?

- The identification of coronary heart disease is frequently delayed or undiagnosed in women, and many at risk for adverse outcomes are not offered preventive or therapeutic options.
- This underrecognition may be due partly to more prevalent nonobstructive coronary heart disease in women, with microvascular dysfunction largely contributing to myocardial ischemia.
- Whether adding retinal imaging to further risk stratify low-risk women will result in the attenuation of risk of death or morbidity from atherosclerotic cardiovascular disease events in this group, which would be unrecognized using current practice guidelines, remains to be determined.

Coronary and cerebral microvascular disease is associated with significant cardiovascular morbidity with respect to incident coronary heart disease (CHD), ischemic stroke, and congestive heart failure (HF) and mortality from these diseases.[1] The retinal vasculature provides a readily accessible window to assess the microvasculature. With advances in technology, imaging of the fundus is relatively inexpensive, accurate, reproducible, and radiation free. The retinal arterioles (measured as the central retinal arteriolar equivalent [CRAE]), retinal venules (measured as the central retinal venular equivalent [CRVE]), and retinal microvascular abnormalities have been associated with atherosclerotic cardiovascular disease events (ASCVEs; defined as incident CHD and ischemic stroke)[2–4]: incident CHD,[5–8] particularly in women, incident stroke,[6,9–13] and cardiovascular mortality.[7,14–17] Although fundus photography has been recognized as a promising imaging modality to evaluate the pathogenesis of cardiovascular diseases, its ability to be applied as a test to predict ASCVEs in the clinical setting has yet to be evaluated with current practice guidelines.

In the 2013 guideline on the assessment of cardiovascular risk, the American College of Cardiology/American Heart Association (ACC/AHA) released Pooled Cohort Equations (PCEs), multivariable risk equations developed to predict 10-year risk of ASCVEs, derived from data from multiple cohort studies, including ARIC (Atherosclerosis Risk in Communities), CARDIA (Coronary Artery Risk Development in Young Adults), and CHS (Cardiovascular Health Study), in part to include the outcome of ischemic stroke in treatment guidelines and to address the limitations of the Framingham Risk Score and its application to the ATP (Adult Treatment Panel Guidelines) III.[18] The ACC/AHA simultaneously published the guideline on the treatment of blood cholesterol, creating new standards to guide statin therapy. Although previous ATP III guidelines generally recommended statin therapy for patients whose estimated 10-year Framingham Risk Score was >20% for a CHD event, the new guidelines recalibrate the threshold for treatment, recommending statin therapy for adults whose 10-year ASCVE risk is >7.5%.

Our study aimed to elucidate the association of retinal vessel calibers with long-term cardiovascular outcomes and death in an average 16-year follow-up in a closely followed, well-adjudicated, large population cohort of asymptomatic adults in the ARIC Study and to assess the incremental value of retinal vessel calibers to the 2013 ACC/AHA PCE risk score.

METHODS

Study Design and Study Population

The ARIC Study is an ongoing, prospective, observational study of atherosclerosis risk factors in 4 US communities (Forsyth County, North Carolina; Jackson, MS; suburbs of Minneapolis, MN; and Washington County, Maryland) originally made up of 15 792 men and women between 45 to 64 years recruited between 1987 and 1989 (visit 1).[19] The participants were examined initially every 3 years, with the second examination in 1990 to 1992, the third in 1993 to 1995, the fourth in 1996 to 1998, and the fifth in 2011 to 2013. The Institutional Review Board at each participating site approved the study protocol, and informed consent was obtained in writing at each examination.

Identification of Cardiovascular Outcomes and Death

Outcomes evaluated in this study are incident ischemic stroke, CHD, HF, and death subsequent to the third visit until the end of 2012 (average, 16-year follow-up). The methodology for

quality control, detection, and adjudication of CHD events has been presented previously.[20] Trained abstractors retrieved information on out-of-hospital deaths via death certificates, hospitalized patients, physician questionnaires, and next-of-kin interviews. We defined ASCVEs as new ischemic stroke (fatal or nonfatal) or incident CHD as previously described[21]: acute (definite or probable) myocardial infarction (MI), fatal CHD, silent MI, and myocardial revascularization, including coronary angioplasty or coronary artery bypass graft surgery from the third visit (1993–95) until the end of 2012 among subjects who were free of these outcomes and HF at the beginning of visit 3 when retinal photography was performed. Incident HF was defined by HF hospitalization or HF death, according to the *International Classification of Diseases–Ninth Revision* code 410 in any position, obtained by ARIC Study retrospective surveillance of hospital discharges.[22,23]

Measurement of Retinal Vessel Calibers

Retinal fundus photographs were taken at the third examination (1993–1995), which 12 887 participants attended, and retinal vessel calibers were measured as CRAE, CRVE, and arteriolar-to-venular diameter (A/V) ratio (A/V ratio=CRAE/CRVE). A/V ratio eliminates the denominator for arteriolar and venular measurements and thus magnification differences between photographs. However, because these 2 measures may represent distinct processes, the A/V ratio analysis is presented in the online-only Data Supplement Tables. After 5 minutes of adaptation to the dark, 1 random eye was selected, and a 45° retinal photograph was taken. Photographs were digitized, and trained and masked graders measured the caliber of individual arterioles and venules running through an area one-half to 1 disk diameter from the optic disk margin. CRAE and CRVE were calculated, representing the average of estimated calibers for the central retinal vessels. The reproducibility for CRAE and CRVE based on repeat readings of the same fundus photograph was excellent, as previously reported.[24]

Components of the ACC/AHA PCE Risk Score and Multivariate Models

Age, sex, race (self-reported), total cholesterol (measured by blood plasma assay), high-density lipoprotein (measured by blood plasma assay), systolic and diastolic blood pressures (measured 3 times with a random-zero sphygmomanometer with the average of the second and third measurements used for analysis), hypertension status (defined as antihypertensive medication use within the past 2 weeks of examination, either self-reported or taken from prescription bottles), diabetes mellitus status (defined on the basis of use of antidiabetic medications, self-report of a physician diagnosis, fasting glucose value ≥126 mg/dL, or nonfasting glucose ≥200), and current smoking status (self-reported) were analyzed. Unadjusted and multivariate models for CRAE and CRVE also included correction for retinal photography magnification.

Statistical Analysis

Of 12 887 participants who attended visit 3, 1854 were excluded for nongradable or missing retinal photographs; another 500 were excluded for previous stroke, MI, or congestive HF; and ≈63 had insufficient data to calculate ACC/AHA PCE risk score (ie, race other than black or white), leaving 10 470 for analysis. As previously reported, those individuals with ungradable or missing retinal photographs were more likely to be older, black, hypertensive, diabetic, and of higher cardiovascular risk.[25] A/V ratio and magnification-adjusted CRAE and CRVE were analyzed as a continuous and as categorical variables, respectively (population quartiles, with the first quartile representing the narrowest arterioles and/or venules and the fourth quartile representing the least narrow arterioles and/or widest venules). Magnification-adjusted CRAE was calculated as the residual value after fitting a linear regression model with CRAE as the outcome and CRVE as the predictor. Magnification-adjusted CRVE was calculated similarly. Baseline characteristics were summarized with the use of descriptive statistics for continuous variables and number counts and percentages for categorical variables. Linear regression and χ^2 tests for trend were used to test for a relationship between continuous or categorical baseline characteristics with quartiles of CRAE and CRVE. Incident risk was calculated for each outcome. Follow-up time was calculated as the time from the third examination to the time of the first event. Hazard ratios were calculated with Cox proportional hazards regression. Two multivariate models investigating the association between A/V ratio quartiles and outcomes were created, 1 adjusting for age, race, and sex and the second adjusting for the components of the PCEs: age, race, sex, smoking, diabetes mellitus, systolic blood pressure, hypertension treatment, high-density lipoprotein, and total cholesterol. Ten- and fifteen-year risks of events were calculated for each outcome on the basis of Kaplan-Meier failure curves.

To assess the incremental value of retinal vessel caliber to the 2013 ACC/AHA PCE risk score, 2 models of ASCVE risk were created: model 1, 10-year risk of ASCVEs for each subject at visit 3 per 2013 ACC/AHA PCEs[26]; and model 2, model 1 plus CRAE, CRVE, or A/V ratio quartiles. Individuals were classified into low, intermediate, and high risk using the risk thresholds of <5%, 5% to 7.5%, and >7.5% for each of these models. To assess reclassification, we computed the continuous net reclassification improvement.[27] The population was further stratified by PCE risk group and CRAE, CRVE, or A/V ratio quartiles to assess the performance of these measures in subgroups of women on the basis of risk score. To define improvement in model discrimination with the addition of CRAE, CRVE, or A/V ratio quartiles in women, the Harrell C statistic was calculated for ASCVE risk for the base model and the base model plus CRAE, CRVE, or A/V ratio within risk subgroups.

All data were analyzed with STATA version 14.0.

RESULTS

Those subjects with a wider retinal venules or narrower retinal arterioles were more likely to be older, male, and black; to have diabetes mellitus; to be on antihypertension medications; and to have higher systolic blood pressure, higher total cholesterol, and lower high-density lipoprotein (Table 1). The mean length of follow-up was 16 years, during which time there were 1779 incident

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Table 1. Baseline Characteristics of Subjects in the ARIC Study Cohort Stratified by Retinal Vessel Caliber Quartiles (N=10 470)

Characteristic	CRVE Quartiles Venular Widening →					CRAE Quartiles Arteriolar Narrowing →				
	1 (n=2618)	2 (n=2617)	3 (n=2618)	4 (n=2617)	*P* Value	4 (n=2617)	3 (n=2618)	2 (n=2617)	1 (n=2618)	*P* Value
Age, mean (SD), y	60±5.6	60±5.7	59±5.5	59±5.5	<0.001	59±5.6	60±5.5	60±5.6	60±5.6	0.001
Men, n (%)	920 (35)	1075 (41)	1218 (47)	1305 (50)	<0.001	915 (35)	1071 (41)	1183 (45)	1349 (52)	<0.001
Black, n (%)	337 (13)	437 (17)	622 (24)	836 (32)	<0.001	485 (19)	556 (21)	605 (23)	586 (22)	<0.001
Smoking, current, n (%)	258 (10)	385 (15)	492 (19)	712 (27)	<0.001	539 (21)	440 (17)	438 (17)	430 (16)	<0.001
Diabetes mellitus, n (%)	285 (16)	340 (14)	369 (14)	451 (14)	<0.001	344 (13)	353 (14)	359 (14)	389 (15)	0.07
Treated hypertension, n (%)	642 (25)	696 (27)	794 (30)	904 (35)	<0.001	556 (21)	671 (26)	849 (32)	960 (37)	<0.001
SBP, mean (SD), mm Hg	121±19	123±19	125±18	127±19	<0.001	116±17	122±17	126±18	131±18	<0.001
TChol, mean (SD), mg/dL	207±36	207±37	208±37	210±39	0.002	207±36	208±38	208±37	209±38	0.1
HDL, mean (SD), mg/dL	55±19	53±18	52±18	51±18	<0.001	54±18	53±18	53±18	52±19	<0.001
BMI, mean (SD), kg/m^2	29±6	29±6	28±6	28±6	<0.001	28±5	28±5	29±5	29±6	<0.001

ARIC indicates Atherosclerosis Risk in Communities; BMI, body mass index; CRAE, central retinal arteriolar equivalent; CRVE, central retinal venular equivalent; HDL, high-density lipoprotein; SBP, systolic blood pressure; and TChol, total cholesterol.

CHD events, 548 ischemic strokes, 1395 HF events, and 2793 deaths. Rates of all outcomes considered were higher in participants with wider retinal venules (CRVE) and narrower retinal arteries (CRAE; Table 2). There was no evidence of nonlinearity when restricted cubic splines were used to evaluate outcomes. CRAE

Table 2. Hazards Ratios of Ischemic Stroke, All-Cause Mortality, HF, Incident CHD, and ASCVEs per 1-SD Decrease in CRAE and 1-SD Increase in CRVE

Combined Cohort (n=10 470)						
Event	Adjustment*	Events, n	HR (95% CI) per 1-SD Decrease in CRAE	*P* Value	HR (95% CI) per 1-SD Increase in CRVE	*P* Value
Ischemic stroke	Unadjusted	548	1.36 (1.23–1.50)	<0.001	1.34 (1.21–1.47)	<0.001
	Multivariate		1.14 (1.03–1.26)	0.013	1.18 (1.07–1.31)	0.001
Death	Unadjusted	2793	1.19 (1.14–1.25)	<0.001	1.24 (1.18–1.29)	<0.001
	Multivariate		1.06 (1.01–1.11)	0.020	1.13 (1.08–1.18)	<0.001
HF	Unadjusted	1395	1.17 (1.10–1.24)	<0.001	1.19 (1.11–1.26)	<0.001
	Multivariate		1.00 (0.94–1.07)	0.908	1.05 (0.99–1.12)	0.10
Women (n=5952)						
CHD	Unadjusted	655	1.23 (1.13–1.35)	<0.001	1.26 (1.15–1.38)	<0.001
	Multivariate		1.13 (1.03–1.24)	0.012	1.10 (1.00–1.20)	0.04
ASCVE	Unadjusted	862	1.26 (1.17–1.37)	<0.001	1.27 (1.17–1.38)	<0.001
	Multivariate		1.14 (1.05–1.24)	0.002	1.12 (1.03–1.21)	0.005
Men (n=4518)						
CHD	Unadjusted	1124	1.07 (1.00–1.15)	0.058	1.09 (1.02–1.17)	0.014
	Multivariate		0.98 (0.91–1.06)	0.63	1.02 (0.95–1.10)	0.60
ASCVE	Unadjusted	1294	1.11 (1.04–1.18)	0.002	1.12 (1.05–1.20)	0.001
	Multivariate		1.00 (0.93–1.07)	0.93	1.04 (0.97–1.11)	0.27

CHD and ASCVE were tested separately in men and women because of a significant sex interaction (*P*=0.02 for both). ASCVE indicates atherosclerotic cardiovascular disease event; CHD, coronary heart disease; CI, confidence interval; CRAE, central retinal arteriolar equivalent; CRVE, central retinal venular equivalent; HF, heart failure; and HR, hazard ratio.

*Multivariate model including age, race, SBP, cigarette use, TChol, HDL, DM, and HTN meds.

and CRVE were significantly associated with death (P=0.02 and P<0.0001, respectively) and ischemic stroke (P<0.0001 for both) after adjustment for the PCE variables (Figure 1). The relationship between CRAE and CRVE and HF outcomes was nonsignificant after multivariate adjustment, primarily by the addition of systolic blood pressure to the model (Table 2 and Figure 1). We observed a significant interaction of sex with incident CHD and ASCVEs (P=0.02 for both) but not for death, HF, or stroke (P>0.2 for all 3). Accordingly, separate sex analysis was performed for CHD and ASCVEs. There was also a nominally significant interaction between CRAE/CRVE and diabetic status. However, this interaction was not apparent when the analysis was restricted to the female subgroup. After adjustment for the PCE variables, CRAE and CRVE were significantly associated with CHD and ASCVEs in women but not men (Table 2 and online-only Data Supplement Table I). This differential relationship persisted after adjustment for PCE variables (Table 2 and Figure 1), remaining significant in women but not in men (CRAE, P=0.005 and P=0.933; CRVE, P<0.0001 and P=0.354, respectively). In addition, body mass index was not significant when added to the multivariate model, and CRAE and CRVE remained independently associated with CHD and ASCVEs. The association of the composite measure of A/V ratio (CRAE/CRVE) with cardiovascular outcomes was equivalent to those described for the individual measures (online-only Data Supplement Tables II and III).

To test whether CRVE and CRAE may add incremental value to the PCE risk score in the female population, we began by assessing reclassification. Despite no improvement in the integrated discrimination improvement index, category-free net reclassification yielded a net reclassification of 6.0% (95% confidence interval [CI], −0.4 to 11.1; P=0.06 for CRVE), 7.6% (95% CI, 2.3–12.2; P=0.040 for CRAE), and 8.1% (95% CI, 2.8–12.8; P=0.007 for A/V ratio). The 10-year risk for each PCE risk group, using categories of <5%, 5% to 7.5%, and >7.5%, was within the expected range for each group: 3.9% for the low-risk group (<5% PCE risk score), 7.4% for the intermediate-risk group (5%–7.5% PCE risk score), and 16.9% for the high-risk group (>7.5% PCE risk score; Table 3). To further test how CRVE and CRAE may be clinically useful, women were classified into ACC/AHA PCE risk categories according to their estimated 10-year risks, and CRVE or CRAE quartiles were then used to further stratify the women within these risk categories (Table 3). Further stratification by both measures provided additional discrimination in low-risk women but not in the intermediate- or high-risk groups (P≤0.001 for CRVE and CRAE; Table 3). For example, for CRAE, the smallest quartile had a significantly higher risk of ASCVEs compared with the highest quartile within the subset of women originally classified as low risk (hazard ratio, 1.95; P<0.001; Table 3 and Figure 2A). Although the observed overall 10-year risk in the low-risk group was 3.9%, the low-risk women with the narrowest arterioles experienced a 10-year event rate of 5.6% compared with 2.8% for those with the widest arterioles (5.6% versus 2.8% for narrower versus wider CRAE; 5.0% versus 3.4% for wider versus narrower CRVE; Table 3 and Figure 2A and 2B). Qualitatively, the same result, that is, retinal measures provide further risk stratification only in otherwise low-risk women and not in medium- and high-risk women, can be seen when quartiles of CRAE/CRVE specific to low-risk women are used (Table 4) rather than quartiles derived from all women. Stratification of low-risk women with the A/V ratio yielded similar results (online-only Data Supplement Table IV). When inverse probability weighting was used to account for differential rates of missing retinal photographs driven by previously identified risk factors, no major study findings differed.

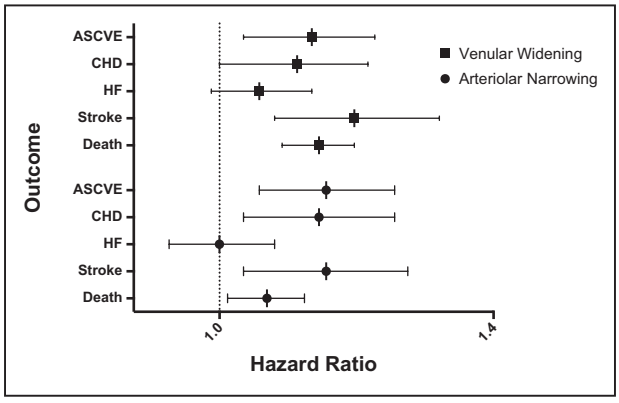

Figure 1. Risk of death and atherosclerotic cardiovascular events (ASCVEs).
Risk of death and ASCVEs per 1-SD widening of the retinal vein or narrowing in the retinal artery in the Atherosclerosis Risk in Communities Study cohort (n=10 470) assessed by fundus photography after multivariate adjustment for the components of the Pooled Cohort Equations risk score (age, sex, race, systolic blood pressure, total cholesterol, high-density lipoprotein, hypertension, diabetes mellitus, cigarette use). Coronary heart disease (CHD) and ASCVEs represent incident CHD risk in women only (n=5952). HF indicates heart failure.

DISCUSSION

In this large, multiracial, prospective cohort study, arteriolar and venular retinal vessel calibers, as assessed on fundus photography, were associated with all-cause mortality and ischemic stroke in both sexes and with CHD in women after a mean follow-up of 16 years. The association between retinal vessel calibers and incident HF was nonsignificant after adjustment for systolic blood pressure. Narrower retinal arterioles and wider venules conferred higher risk for ASCVEs in women and provided incremental value above and beyond the ACC/AHA PCE

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Table 3. Estimated ASCVE Rates and Cumulative 10- and 15-Year Hazard Ratios in Women (n=5952) Stratified by PCE Risk Score and CRAE and CRVE Quartiles

PCE Risk Group	10-y Risk (95% CI)	15-y Risk (95% CI)	C Statistic*	Quartile	N	n	10-y Risk (95% CI)	15-y Risk (95% CI)	HR (*P* Value)
Arteriolar narrowing (CRAE)									
<5% (n=3277)	3.9 (3.2–4.6)	6.4 (5.6–7.3)	0.57	1	682	73	5.6 (4.1–7.6)	8.6 (6.7–11)	1.95 (<0.001)
				2	766	64	4.2 (2.9–5.9)	7.3 (5.6–9.4)	1.49 (0.03)
				3	874	65	3.4 (2.4–4.9)	6.2 (4.8–8.1)	1.32 (0.13)
				4	955	55	2.8 (1.9–4.1)	4.4 (3.2–5.9)	Reference
5%–7.5% (n=956)	7.4 (5.9–9.3)	12.6 (11–15)		1	260	39	9.6 (6.5–14)	12.7 (9.1–18)	*P* trend=0.8
				2	281	41	6.6 (4.2–10)	13 (6.7–14)	
				3	232	36	7.1 (4.4–11)	12.8 (9.8–18)	
				4	183	27	5.8 (3.1–11)	11 (7.0–17)	
>7.5% (n-1719)	16.9 (15–19)	24.8 (23–27)		1	546	146	18 (15–22)	26 (22–30)	*P* trend=0.7
				2	441	116	14 (11–18)	25 (21–30)	
				3	382	109	18 (14– 22)	25 (21–30)	
				4	350	91	17 (13–22)	23 (19–28)	
Venular widening (CRVE)									
<5% (n=3277)	3.9 (3.2–4.6)	6.4 (5.6–7.3)	0.56	4	683	73	5.0 (3.6–6.9)	9.0 (7.1–12)	1.78 (0.001)
				3	803	57	3.8 (2.7–5.4)	5.7 (4.3–7.6)	1.16 (0.42)
				2	864	70	3.5 (2.4–4.9)	6.7 (5.2–8.7)	1.35 (0.09)
				1	927	57	3.4 (2.4–4.8)	4.8 (3.6–6.4)	Reference
5%–7.5% (n=956)	7.4 (5.9–9.3)	12.6 (11–15)		4	262	45	9.5 (6.5–14)	14 (10–19)	*P* trend=0.7
				3	261	27	5.5 (3.3–9.2)	11 (7.4–15)	
				2	220	33	7.0 (4.3–11)	11 (7.4–16)	
				1	213	38	7.4 (4.5–12)	15 (10–20)	
>7.5% (n=1719)	16.9 (15–19)	24.8 (23–27)		4	543	156	21 (17–25)	28 (24–32)	*P* trend=0.3
				3	424	97	12 (9.5–16)	21 (17–25)	
				2	404	122	18 (15–22)	27 (22–31)	
				1	348	87	15 (11–19)	22 (18–27)	

ASCVE indicates atherosclerotic cardiovascular disease event; CI, confidence interval; CRAE, central retinal arteriolar equivalent; CRVE, central retinal venular equivalent; HR, hazard ratio; and PCE, Pooled Cohort Equation.

*Calculated Harrell C statistic of PCE risk groups when CRAE or CRVE is applied.

risk score in low-risk women, a large but understudied group. Low-risk women in the narrowest arteriolar quartile were twice as likely to suffer an ASCVE and ≈4-fold as likely to die of a CHD event as were those in the widest quartile. Using data from retinal vessel imaging in addition to the PCE would result in 11% of all women (8.5% of total ASCVEs in women) being identified at higher risk for ASCVEs who would otherwise not be recognized with current practice guidelines. Our results were robust, replicated with the use of quartiles of CRAE or CRVE specific to low-risk women or all women and when quartiles of A/V ratio were used.

Both arteriolar narrowing and venular dilation are part of the pathological changes that occur within microvascular beds in both hypertensive and atherosclerotic disease.[28] Our data support that retinal arteriolar narrowing and venular dilatation are indeed associated with long-term cardiovascular outcomes. Prior reports have suggested that retinal microvascular disease was associated with cardiac mortality[7,14–17] but not necessarily all-cause death. In addition, retinal vascular calibers have been associated with incident stroke[6,9–13,29,30] and incident CHD,[5–8] particularly in women and primarily after short-term follow up. Retinal vascular caliber has not previously been found to be associated with incident HF but has been associated with left ventricular remodeling as assessed by cardiac magnetic resonance imaging.[31] In the ARIC Study population, our findings show an inter-

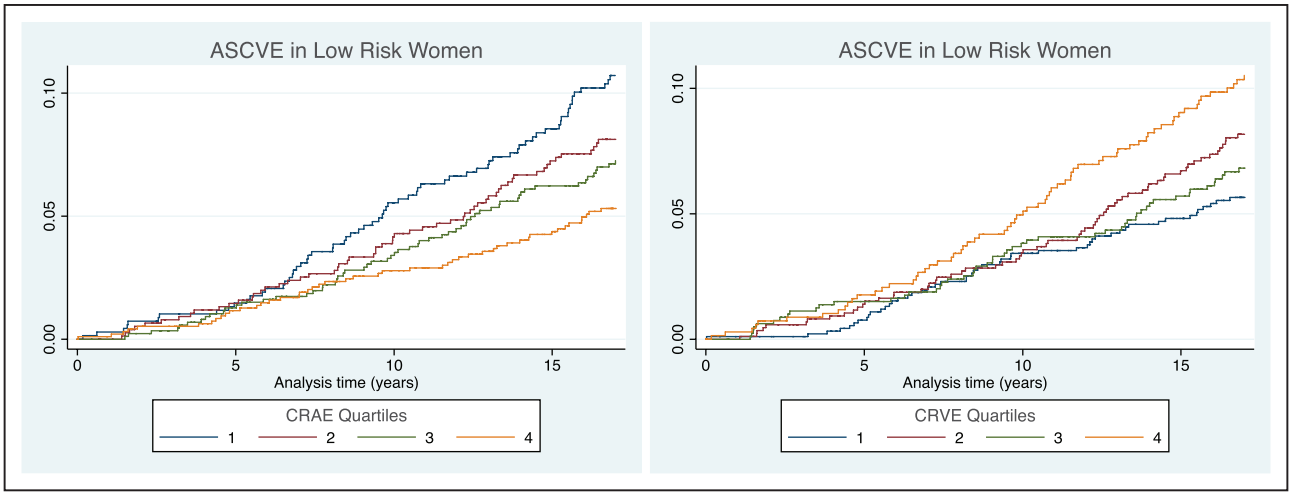

Figure 2. Kaplan-Meier failure curves of atherosclerotic cardiovascular event (ASCVE) risk by central retinal arteriolar equivalent (CRAE) or central retinal venular equivalent (CRVE).
Kaplan-Meier failure curves of ASCVE risk by central retinal arteriolar equivalent CRAE or CRVE quartiles in women with predicted 10-year ASCVE risk <5% according to the American College of Cardiology/American Heart Association Pooled Cohort Equations risk score (low risk, n=3277) in the Atherosclerosis Risk in Communities Study cohort. The first quartile represents the narrowest arterioles and venules, and the fourth quartile represents the least narrow arterioles and widest venules. For CRAE quartiles, the log-rank *P*=0.0001; for CRVE quartiles, the log-rank *P*=0.004.

relationship between microvascular and macrovascular dysfunction; the latter, expressed by elevated systolic blood pressure, seems to be important in the clinical manifestation of HF.

In the differentiation between the retinal measures presented in this work, there are some findings worth noting. CRAE and A/V ratio seem to slightly outperform CRVE in predicting ASCVEs in all women and in low-risk women. However, CRVE may be a stronger predictor of death compared with CRAE. Different risk factors have been associated with wider CRVE (ie, inflammatory markers, body mass index, smoking) versus narrower CRAE (ie, age, systolic and diastolic blood pressures, mean arterial blood pressure).[32,33] These separate pathophysiological underpinnings likely reflect the different strengths of association observed between retinal vessel calibers and cardiovascular outcomes herein. Because CRAE and CRVE may reflect different disease processes, both measures are apparently useful to provide an overall assessment of the risk profile.

CHD poses a significant public health problem in women: It is the primary cause of death in this group, with rates of fatal CHD in women <55 years of age climbing.[34,35] The expression of female-specific ischemic CHD is unlike its male counterpart: It is more often nonobstructive in nature with a larger burden of coronary microvascular disease[36,37] and greater morbidity and mortality.[34,38] In a prior analysis of ARIC data, reduced retinal A/V ratio was predictive of incident CHD (average follow-up time, 3 years) in women but not men after adjustment for traditional risk factors, a finding that has also been observed in meta-analyses.[5,21,39] The present study provides longer-term follow-up and demonstrates the incremental predictive value of retinal vessel calibers to our current practice guidelines, demonstrating that they offer significant additional information above and beyond the PCE risk score to low-risk women. Thirty percent of ASCVEs occurred in low-risk women, a group that represents the majority (55%) of the female ARIC Study population, as is the case for the general female population for which the PCEs would be applied. The majority of US women 40 to 79 years of age (per National Health and Nutrition Examination Survey 2007–2010 data) would be classified as low risk by the PCE risk score (67% of women compared with 40% of men).[26] Compared with low-risk women in the widest arteriolar quartile, those in the narrowest quartile were twice as likely to suffer an ASCVE.

Furthermore, our data suggest that ASCVEs in low-risk women with microvascular dysfunction are more deadly than in women without microvascular dysfunction as assessed by retinal imaging. Because this portion of the population would not typically know that they are at increased risk for cardiovascular disease and often have atypical presenting symptoms, it may represent a group that would particularly benefit from disease prevention education, lifestyle modification, and therapeutic intervention from healthcare providers. Prior work has shown that retinal arteriolar narrowing is reversible by antihypertensive therapy.[40] Therefore, serial monitoring of retinal vessel calibers by fundus photography could potentially provide a secondary end point and visual aid to assist in patient motivation and compliance to dietary, exercise, and therapeutic interventions. In recent

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Table 4. Sensitivity Analysis Based on Quartiles Defined Separately for Risk: Estimated ASCVE Rates and Cumulative 10- and 15-Year Hazard Ratios in Women (n=5952) Stratified by PCE Risk Score and CRAE and CRVE Quartiles Defined Separately for Each PCE Risk

PCE Risk Group	10-y Risk (95% CI)	15-y Risk (95% CI)	C Statistic*	Quartile	N	n	10-y Risk (95% CI)	15-y Risk (95% CI)	HR (*P* Value)
Arteriolar narrowing (CRAE)									
<5% (n=3277)	3.9 (3.2–4.6)	6.4 (5.6–7.3)	0.56	1	820	81	5.1 (3.8–6.9)	7.7 (6.1–9.8)	1.92 (<0.001)
				2	819	70	4.3 (3.1–5.9)	7.6 (5.9–9.7)	1.65 (0.009)
				3	819	62	3.5 (2.4–5.0)	6.1 (4.6–8.0)	1.43 (0.1)
				4	819	44	2.5 (1.6–3.8)	4.2 (3.0–5.9)	Reference
5%–7.5% (n=956)	7.4 (5.9–9.3)	12.6 (11–15)		1	239	37	9.7 (6.4–14)	12.9 (9.1–18)	1.09 (0.7)
				2	239	37	8.2 (5.3–13)	14.2 (10–20)	1.05 (0.8)
				3	239	33	6.1 (3.6–10)	11.7 (8.1–17)	0.93 (0.8)
				4	239	36	5.7 (3.3–11)	11.5 (7.9–17)	Reference
>7.5% (n=1719)	16.9 (15–19)	24.8 (23–27)		1	430	120	20.0 (16–24)	27.9 (24–33)	1.13 (0.3)
				2	430	98	11.2 (8.5–15)	21.5 (18–26)	0.85 (0.2)
				3	430	130	19.4 (16–24)	26.8 (23–31)	1.20 (0.2)
				4	429	114	16.9 (14–21)	23.1 (19–28)	Reference
Venular widening (CRVE)									
<5% (n=3277)	3.9 (3.2–4.6)	6.4 (5.6–7.3)	0.55	4	819	87	5.0 (3.7–6.8)	8.7 (6.9–11)	1.63 (0.005)
				3	819	60	3.7 (2.6–5.3)	6.2 (4.7–8.2)	1.09 (0.6)
				2	819	55	2.9 (1.9–4.3)	5.5 (4.1–7.4)	1.02 (0.9)
				1	820	55	3.8 (2.6–5.3)	5.2 (3.8–7.0)	Reference
5%–7.5% (n=956)	7.4 (5.9–9.3)	12.6 (11–15)		4	239	45	10.4 (7.1–15)	15.5 (11–21)	1.11 (0.6)
				3	239	26	5.6 (3.3–9.4)	11.3 (7.8–16)	0.62 (0.06)
				2	239	30	6.1 (3.6–10)	9.3 (6.2–14)	0.69 (0.1)
				1	239	42	7.4 (4.7–12)	14.2 (10–20)	Reference
>7.5% (n=1719)	16.9 (15–19)	24.8 (23–27)		4	429	123	21.5 (18–26)	27.9 (28–40)	1.15 (0.3)
				3	430	106	13.7 (15–1)	23.5 (22–32)	0.92 (0.5)
				2	430	115	15.9 (16–3)	23.3 (24–34)	0.99 (0.3)
				1	430	118	16.5 (16–23)	24.5 (24–35)	Reference

ASCVE indicates atherosclerotic cardiovascular disease event; CI, confidence interval; CRAE, central retinal arteriolar equivalent; CRVE, central retinal venular equivalent; HR, hazard ratio; and PCE, Pooled Cohort Equation.

*Calculated Harrell C statistic of PCE risk groups when CRAE or CRVE is applied.

European Society of Cardiology guidelines, several new, simple markers were suggested that could specifically improve ASCVE risk prediction in women, including history of preeclampsia or pregnancy-induced hypertension, gestational diabetes, and polycystic ovary syndrome. Although these markers typically forewarn of later illness (preeclampsia increases risk for hypertension and diabetes mellitus; gestational diabetes increases the risk for diabetes mellitus, etc), it has yet to be established whether they predict ASCVEs independently of the conventional risk factors that they predispose to in the ARIC Study population. A particular advantage of using retinal imaging over these options is the possibility of "requantifying" risk and response to lifestyle interventions via ≈5-year measures.

Retinal arteriolar narrowing serves as an early marker of systemic microvascular dysfunction, and prior work has shown an association between smaller retinal arteriolar caliber and lower hyperemic myocardial blood flow and perfusion reserve.[41] Coronary microvascular dysfunction is frequently present in the absence of epicardial atherosclerosis (particularly in women), and nonobstructive microvascular disease is an independent risk factor for adverse cardiovascular events.[42,43] Interestingly, the relationship between retinal vessel caliber and myocardial blood flow and perfusion reserve was observed only in

those subjects without coronary calcification, suggesting that these measures were less reflective of the coronary microvascular processes in more advanced epicardial coronary disease.[41] Presumably, the contribution of the microcirculation to myocardial perfusion is significantly reduced in the presence of epicardial stenosis, either from restriction of downstream myocardial blood flow or by endothelial dysfunction diminishing flow-dependent vasodilation. In our work, we found retinal vessel caliber to be a better predictor of ASCVEs in women, most likely for 2 reasons: Female-specific ischemic CHD is frequently nonobstructive with a larger encumbrance of coronary microvascular disease compared with ischemic CHD in men,[36,37] and women make up the vast majority of the low-risk PCE category, which is the group in which retinal vessel caliber is best able to discriminate ASCVE risk. Once epicardial coronary disease becomes apparent, as is more often the case in higher-risk men or diabetics, retinal vessel caliber is less likely to be useful in predicting ASCVEs.

This study has several limitations. First, because many retinal photographs were nongradable (however, equally affecting men and women), it is possible that there was a selection bias influencing the observed associations or resulting in an underestimation of risk. However, when inverse probability weighting was used to account for missing data, no major study findings differed. Notably, low-risk individuals, whom these measures are most likely to serve, were less likely to have nongradable photographs. Second, using retinal caliber measurements obtained from 1 randomly selected eye versus the average of both could obscure findings. In clinical practice, retinal photographs could be obtained from both eyes, increasing precision. Third, measurement of retinal vessel size can vary by many factors, including intergrader and intragrader reliability and image quality, leading to an underestimation of risk. These findings need to be replicated in other large cohort studies with well-adjudicated cardiovascular outcomes before these findings are applied on a population level.

CONCLUSIONS

Our study suggests that retinal vessel calibers are associated with long-term cardiovascular outcomes in a large community-based multiracial cohort, particularly in women. These findings suggest that narrower retinal arterioles and wider retinal venules confer a greater risk of death, stroke, HF, and CHD in women. It remains to be replicated whether adding fundus photography to obtain information to further risk stratify women with a PCE risk score <5% will be of benefit in lowering the risk for death or morbidity from ASCVEs in this group, which would not otherwise be recognized with current practice guidelines.

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DISCLOSURES

None.

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FOOTNOTES

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