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Risk Prediction of Coronary Heart Disease based on Retinal Vascular Caliber (From The Atherosclerosis Risk in Communities [ARIC] Study)

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Abstract

Recent studies show that retinal vascular signs such as quantitative retinal vascular caliber are associated with an increased risk of incident coronary heart disease (CHD), but whether these retinal vascular signs add to the prediction of CHD over and above traditional CHD risk factors has not been addressed. We investigated whether these signs add to the prediction of CHD over and above the Framingham risk score amongst people (n=9,155) without diabetes selected from the Atherosclerosis Risk in Communities (ARIC) study. Incident CHD was ascertained using standardized methods and retinal vascular caliber and other retinal signs were measured from retinal photographs. After a mean of 8.8 years of follow up, there were 700 incident CHD events. Women with wider retinal venular caliber (hazard ratio 1.27 per 1 standard deviation increase [95% confidence interval, 1.08, 1.50]) and narrower retinal arteriolar caliber (1.31 per 1 standard deviation decrease [1.10, 1.56]) had a higher risk of incident CHD after adjusting for the Framingham risk score variables. The area under the receiver operator characteristic curve increased from 0.695 to 0.706 (1.7% increase) with the addition of retinal vascular caliber to the Framingham risk model. The risk prediction models with and without the retinal vascular caliber both fitted the data and were well calibrated for women. In men, retinal vascular caliber was not associated with CHD risk after adjustment. Other retinal vascular signs were not associated with 10-year incident CHD in men or women. In conclusion,

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although retinal vascular caliber independently predicts CHD risk in women, the incremental predictive ability over that of the Framingham model is modest, and unlikely to translate meaningfully into clinical practice.

Keywords

Coronary disease; retinal vascular disease; retinal imaging; risk prediction

Introduction

In this paper, we investigate whether retinal vascular caliber (retinal arteriolar narrowing, venular dilatation) and other retinal signs (focal arteriolar narrowing, arterio-venous nicking and retinopathy) add to the prediction of coronary heart disease (CHD) above that already predicted by the variables in the Framingham risk score. We also examine whether any increase in risk predicted by retinal vascular changes would lead to a change in the recommended treatment strategy for CHD. We restricted our analysis to people without diabetes as current treatment guidelines for the prevention of CHD assign people with diabetes to the highest risk category,[1] and additional information from retinal vascular signs would not change this categorization. The current analysis extends our previous analysis which reported only on the association between arteriole to venule ratio (AVR) and 3-year incident CHD, and which also included people with diabetes.[2]

METHODS

The Atherosclerosis Risk in Communities (ARIC) study included a cohort of 15,792 women and men selected in 1987 through 1989 as probability samples of 45–64 year old residents of four US communities: Forsyth County, NC; Jackson, MS (blacks only); suburbs of Minneapolis, MN; and Washington County, MD.[3] Detailed protocols and differences between participants and non-participants have been described elsewhere.[4] The current study is based on the 12,887 participants (86% of survivors) who attended the third examination at which retinal photographs were taken and which took place 6 years after the start of the study (1993–95). Participants were followed-up until 31 December 2003. Of those who attended the third visit, we excluded: 38 whose race was neither black nor white; 42 nonwhite residents in Minneapolis and Maryland; 245 with no retinal photographs; 26 with retinal vascular occlusions; 1,302 who had ungradable photographs for retinal vascular caliber and other retinal signs, or had missing data recorded for any of the risk factors studied; 605 with pre-existing CHD at the third examination and 1,474 people with diabetes mellitus, defined as a fasting blood glucose concentration >7.0 mmol/L, a non-fasting value >11.1 mmol/L, or a self-reported history of treatment for diabetes, at any examination. In total, 9,155 (71% of those who attended the third examination) participants contributed data for this paper.

Institutional Review Boards at each study site approved the study, and written informed consent was obtained at each examination.

Retinal photography followed standardized procedures.[5] Briefly, after 5 minutes of dark adaptation, a 45° retinal photograph was taken of one randomly selected eye. These photographs were digitized and the caliber of individual arterioles and venules coursing through a region one half to 1 disk diameter from the optic disk margin were measured using a computer assisted method by trained, masked graders.[5] These measurements were summarized as the central retinal arteriolar and venular equivalents, which represented the average of estimated calibers for the central retinal vessels. Trained graders also evaluated photographs for retinopathy lesions, focal narrowing and arteriovenous (AV) nicking according to a standardized protocol[5]. Retinopathy in the present study was defined as the presence of any of the following lesions: microaneurysms, retinal hemorrhages or soft exudates. Reproducibility statistics, based on repeat readings of the same retinal photograph, for these measurements were high.[5,6]

Ascertainment of, and quality control procedures for, CHD events have been described previously.[7] Briefly, trained abstractors retrieved information on hospitalized patients, and out of hospital deaths were investigated by means of death certificates, physician questionnaires and next-of-kin interviews. Incident CHD was defined as acute (definite or probable) myocardial infarction (MI), fatal coronary heart disease, silent MI and myocardial revascularization (e.g. coronary angioplasty or coronary artery bypass graft surgery) among persons without pre-existing CHD at the time of retinal photography at the third examination.[2]

Participants underwent standardized assessments of cardiovascular risk factors at every examination.[3] Cigarette smoking, diabetes, and use of antihypertensive drugs were ascertained from an examiner-administered questionnaire. At each examination blood pressure was measured with a random-zero sphygmomanometer. Measurements of plasma total cholesterol and high-density lipoprotein cholesterol (HDL) are described in detail elsewhere.[8] The measurements of the risk factors at the third examination were used in the analysis, except for blood pressure where the mean of the last two measurements at each of the three visits was used.

We used Cox proportional hazard models to estimate the relative risk of incident CHD associated with a one standard deviation decrease in retinal arteriolar caliber, a one standard deviation increase in venular caliber and with the presence or absence of each of the focal retinal microvascular signs. The retinal vascular caliber analyses were carried out for men and women separately as retinal vascular caliber had previously been shown to predict the 3-year risk of CHD amongst women but not men.[2] We also modelled both retinal vascular calibers together in the same model as this has been found to reduce confounding from the correlated fellow vessel caliber.[9]

The hazard ratios are presented initially adjusted for center, race and other retinal caliber (Model 1) and then adjusted for the variables that make up the Framingham risk score – age, systolic blood pressure, total cholesterol, smoking status and HDL cholesterol (Model 2). The appropriate functional form of each of the continuous variables in the models was assessed using fractional polynomials.[10]

The change in the area under the receiver operator characteristic curve (AUC) was used to measure the improvement in prediction using the method described by Chambless et al which accounts for the censoring in the data.[11] We implemented the method demonstrated to be less biased which utilises Bayes theorem and the estimated survival functions. The increase in the AUC when each retinal microvascular sign was added to the prediction model based on the Framingham risk variables was then calculated. To test whether the increase in the AUC was significant, we created 1,000 bootstrap samples and used the percentile method to estimate the 95% confidence interval for the increase in the AUC. We also used 200 of these bootstrap samples to assess the overestimation of the AUC that may occur when the same dataset is used to develop the model and estimate the AUC.[12] The increase in the AUC with the addition of the AVR was also calculated as a previous analysis of the ARIC data reported an association between AVR and incident CHD.[2]

We evaluated the overall fit of the proportional hazards models using the Grønnesby and Borgan goodness of fit test which groups the subjects' estimated risk score into deciles. The number of observed and expected events within each decile are then compared. The test was implemented using the Wald test method and the calibration of the models was investigated by calculating standardised z-statistics within each risk score decile.[13]

We plotted the ten year risk of incident CHD predicted by the model that included the retinal calibers and the Framingham variables against the risk of CHD predicted by the model that included only the Framingham variables. The predicted risks from the two models were categorised into the three risk groups as described in the National Cholesterol Education Program (NCEP) report (low: <10% risk, intermediate: 10–20% risk and high: >20% risk).[1] Then, for people whose CHD risk category changed, the predicted risk was compared to the observed risk, calculated using the Kaplan-Meier method.[14] All data analyses were performed using SAS v9.1.

The funding sources had no role in the collection, analysis, or interpretation of the data or in the decision to submit the manuscript for publication.

RESULTS

Table 1 shows baseline characteristics of the study population. The mean length of follow-up was 8.8 years, 24% had been followed up for at least ten years and during the follow-up 700 people experienced a CHD event. Three percent of people had retinopathy, 15% had retinal arteriolar focal narrowing and 14% had arteriovenous nicking.

In the proportional hazards models (Table 2), both arteriolar and venular caliber were associated with incident CHD among women. Decreasing arteriolar and increasing venular caliber remained associated with an increased risk of CHD when the Framingham variables were added to the model (Model 2). Among women, there was no evidence of an interaction in Model 2 between the arteriolar and venular calibers ($p = 0.75$).

Among men, arteriolar caliber was associated with incident CHD after adjusting for center, race and retinal venular caliber (Model 1). However, there was no evidence of an association between either retinal arteriolar or venular caliber with CHD after adjusting for the Framingham variables amongst men without diabetes (Model 2). There was a significant interaction between gender and the retinal venular caliber ($p = 0.008$) and between gender and the retinal arteriolar caliber ($p = 0.04$).

None of the other retinal microvascular signs were associated with incident CHD amongst either men or women after adjusting for the Framingham variables (Table 3). There was a significant interaction between gender and focal narrowing ($p = 0.03$), but not between gender and retinopathy ($p = 0.82$) or gender and AV nicking ($p = 0.76$).

The results of the analyses did not change when the systolic blood pressure measured only at the time of the retinal photograph, rather than the average of the systolic blood pressures measured both at the current and at the previous two visits, was used in the Cox models (data not shown).

The highest increase in the AUC was for the inclusion of the arteriolar and venular calibers for women (Table 4) which was also significant ($p<0.05$). The overestimation of the AUC due to using the same data to fit the model and calculate the AUC was estimated to be 0.00009. When the AVR was used instead of the separate arteriolar and venular calibers the increase in the AUC was the same (0.012). The highest incremental gain for any of the other retinal microvascular signs was 0.004 when arteriolar caliber was evaluated alone among women (data not shown).

The goodness of fit tests indicated that the model in women that contained the retinal calibers and the Framingham variables (χ^2_9=8.19, p= 0.52) and the model that included only the Framingham variables (χ^2_9=10.18, p= 0.36) both fitted the data. For both models there were no significant differences between the observed and expected number of events in any of the risk score deciles (Table 5). The p-values were generally higher, indicating better agreement between observed and predicted number of events, in the lower deciles of risk for the model containing the retinal calibers. Conversely, the p-values were generally lower, indicating poorer agreement, in the higher deciles of risk for the model containing the retinal calibers. Women in the first five risk score deciles had a predicted risk of less than 4%.

Figure 1 plots the ten year risk of CHD for non-diabetic women predicted by the model that included the retinal calibers and the Framingham variables against the risk of CHD predicted by the model that included only the Framingham variables. Horizontal and vertical lines have been added at 10% and 20% to indicate the thresholds of predicted risk at which a treatment strategy may change as recommended in the NCEP report.[1] For those women who appear in the sections on the diagonal, their risk category is not changed by the addition of the retinal calibers to the prediction model. For those women who appear in sections off the diagonal, their risk category is changed with the addition of the retinal caliber to the prediction model. There were 196 (4.0%) women whose risk category was changed with the addition of the retinal calibres to the risk prediction model. Nineteen of the women whose risk category was changed experienced a CHD event.

The graph illustrates the trade-offs that would happen if the retinal calibers were added to the prediction model. Although eight women who developed CHD would now be categorised as intermediate risk rather than low risk, there would be nine women who developed CHD who would be reassigned from the intermediate risk group to the lower risk group. The graph also illustrates the small absolute changes in risk that occur with the addition of the retinal caliber to the prediction model. The model containing only the Framingham risk score variables more closely predicted the observed Kaplan-Meier incidence of CHD amongst women whose risk category may change with the addition of the retinal calibers to the prediction model.

DISCUSSION

This study demonstrated that smaller retinal arteriolar and larger venular caliber are associated with an increased 10-year risk of CHD amongst women without diabetes after adjusting for the traditional CHD risk factors included in the Framingham equation. No other retinal microvascular sign was related to the 10-year risk of CHD amongst men or women without diabetes. The increased risk associated with the retinal caliber among women corresponded to a small increase in the AUC (an increase of 1.7%), which suggests that adding information from retinal vascular caliber to the Framingham variables does not improve substantially the discrimination between those who do and do not develop CHD over a 10-year period. There was a slight improvement in the calibration of the prediction model with the addition of the retinal vascular caliber. However, this improvement was among women at low risk (<4%) of CHD and a relatively small number of women were reclassified when we added retinal caliber measurements to the model containing Framingham variables only.

Although the increase in the AUC of 1.7% for the inclusion of the retinal calibers amongst non-diabetic women was small, it compares favourably to other potential predictive factors that have been examined.[15,16] The highest percentage increase in the AUC due to any of the thirty-seven factors examined in these two previous studies was 1.4%. A possible reason why retinal vascular calibers appear to perform better than other non-traditional risk factors in women could be that microvascular disease plays a greater role in CHD in younger women, which may not be adequately captured by the non-traditional risk factors.[17] As compared to men, risk factors such as diabetes and hypertriglyceridemia may confer greater CHD risk in women.[18,19] Further, women often experience CHD symptoms in the absence of obstructive coronary disease,[20–22] suggesting that microvascular disease may possibly play a greater role in CHD pathogenesis in women than in men.[20–22]

Our previous analysis of the ARIC cohort reported and association between AVR and incident CHD among women and we considered this to reflect the effect of narrower arteriolar calibers.[2] The current analysis demonstrates an association between wider venular caliber, as well as narrower arteriolar caliber, and incident CHD. The association of wider venular calibre with CHD has also been observed in the Blue Mountains Eye Study and the Cardiovascular Health Study.[23,24] It has been suggested that the association between wider venular caliber and CHD may reflect the effects of inflammation and endothelial dysfunction on the vascular system.[23,24] This is supported by evidence of associations between wider venular caliber and C-reactive protein[25,26], and between C-reactive protein and incident CHD.[27]

In a recent meta-analysis of studies investigating the relationship between c-reactive protein and CHD, the pooled odds ratio for studies with male participants was similar to the pooled odds ratio for studies with female participants and there was no significant heterogeneity between studies due to the sex of the participants.[27] Hence, the different effects of venular caliber between men and women we have observed in the current analysis are unlikely to be explained by the suggested relationship between wider venular calibers and c-reactive protein.

The strengths and limitations of this study have been discussed previously.[2] Additional limitations include, firstly, retinal vascular data graded from a single photograph of a randomly selected eye is likely to underestimate the prevalence of retinal vascular signs. In a subset of the ARIC study in which retinal photography was repeated, 42% of retinopathy signs present at the third examination were not present 3 years later.[28] The misclassification of the presence of the retinal signs may have contributed to the lack of association reported between these factors and incident CHD. Secondly, measurement of retinal vessel caliber is influenced by factors such as image quality, pulse cycle and inter and intra grader reliability,[6] which increase random measurement error and may lead to an underestimation of risk.[29] Finally, there may be residual confounding from inadequate adjustment for blood pressure. A strength of this study is that the predictive value of the retinal calibers was assessed by evaluating their effect on treatment strategies, as well as changes in discrimination and calibration, as recently recommended,[30] rather than solely in terms of risk increases.

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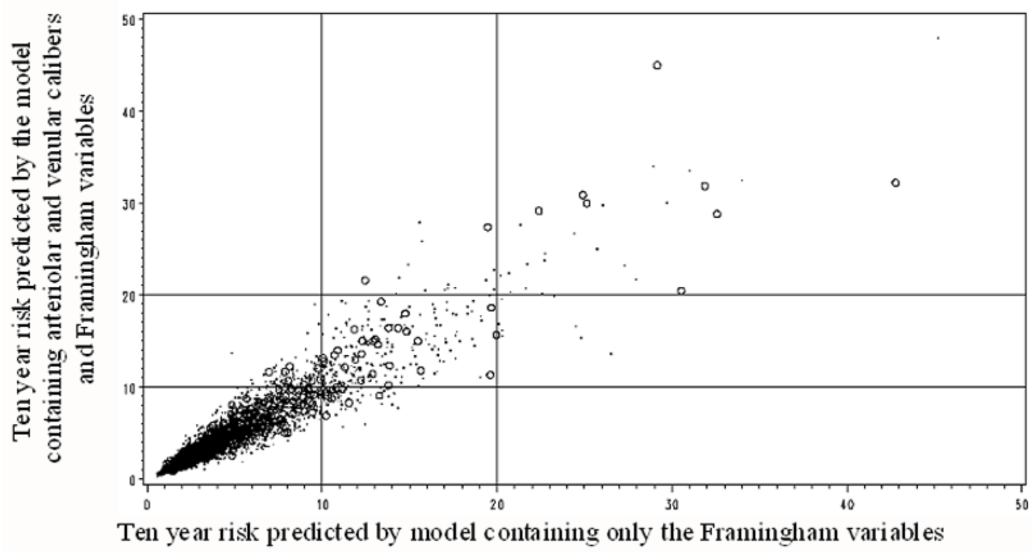

Figure 1.

Ten year risk of incident coronary heart disease predicted by the model containing arteriolar and venular calibers and Framingham variables against risk predicted by the model containing only the Framingham variables

○ = CHD event, ● = censored observation

Table 1

Baseline characteristics of study population, by gender

Variable	Men (n=3826)	Women (n=5329)
Age (mean) (years)	60	59
Black race	17%	22%
Systolic blood pressure (mean) (mm Hg)	121	119
Total cholesterol (mean) (mmol/L)	5.2 (200mg/dl)	5.5 (213mg/dl)
High density lipoprotein (mean) (mmol/L)	1.2 (46mg/dl)	1.6 (60mg/dl)
Current smoker	18%	17%
On anti-hypertensive medications	24%	27%

Table 2

Adjusted risk* of coronary heart disease associated with retinal caliber for men and women without diabetes mellitus

Gender	Retinal vascular caliber	Events/ At risk	Model 1†		Model 2‡	
			Hazard ratio	95% Confidence interval	Hazard ratio	95% Confidence interval
Men	Arteriolar caliber (decreasing)	421/3502	**1.17**	**1.05,1.31**	1.03	0.91,1.16
	Venular caliber (increasing)		1.11	0.99,1.25	1.02	0.90,1.14
Women	Arteriolar caliber (decreasing)	207/4912	**1.43**	**1.21,1.69**	**1.31**	**1.10,1.56**
	Venular caliber (increasing)		**1.47**	**1.25,1.73**	**1.27**	**1.08,1.50**

* Risk is per 1 standard deviation decrease in arteriolar caliber and per 1 standard deviation increase in venular caliber

† Model 1. adjusted for center, race and retinal venular caliber for models for arteriolar caliber (and vice versa)

‡ Model 2. adjusted for center, race and Framingham variables (age, systolic blood pressure, total cholesterol, smoking status and HDL) and retinal venular caliber for models for arteriolar caliber (and vice versa)

Table 3

Adjusted risk of coronary heart disease associated with retinal signs for men and women without diabetes mellitus

				Model 1*		Model 2†	
Retinal sign	**Gender**		**Events/n**	**Hazard ratio**	**95% Confidence interval**	**Hazard ratio**	**95% Confidence Interval**
Retinopathy‡	Men	Present	16/130	1.08	0.66, 1.79	1.02	0.62, 1.69
		Absent	406/3340				
	Women	Present	8/151	1.29	0.64, 2.62	1.09	0.53, 2.22
		Absent	203/4763				
Focal narrowing	Men	Present	89/546	**1.47**	**1.17, 1.86**	1.18	0.93, 1.50
		Absent	352/3087				
	Women	Present	29/742	0.92	0.62, 1.36	0.73	0.49, 1.08
		Absent	183/4358				
Arterio-venous nicking	Men	Present	76/519	1.28	1.00, 1.64	1.16	0.91, 1.49
		Absent	374/3184				
	Women	Present	35/668	1.29	0.90, 1.85	1.08	0.75, 1.56
		Absent	189/4521				

*Model 1. adjusted for center, race and retinal venular caliber for models for arteriolar caliber (and vice versa)

†Model 2. adjusted for center, race and Framingham variables (age, systolic blood pressure, total cholesterol, smoking status and HDL) and retinal venular caliber for models for arteriolar caliber (and vice versa)

‡Includes microaneurysms, retinal hemorrhages or soft exudates

Table 4

Area under the receiver operator characteristic (ROC) curve at ten years for predictive models that included retinal vascular calibers, the Framingham variables and the Framingham variables plus the retinal vascular sign, women without diabetes mellitus

	Area under ROC curve at 10 years			
	Retinal vascular caliber *	Framingham variables*	Framingham plus retinal caliber*	Incremental (%)change in area under ROC curve
Arteriolar and venular calibers	0.600	0.695	0.706	0.012 (1.7)

* centre and race are also included in each of the prediction models

Table 5

Observed and expected number of events by risk score decile among women without diabetes

	Model including Framingham variables*					Model including Retinal Calibers and Framingham variables*				
Risk score decile	**Number at risk**	**Observed**	**Expected**	**z-score**	**p-value**	**Number at risk**	**Observed**	**Expected**	**z-score**	**p-value**
1	491	4	5.8	−0.8	0.4	492	2	5.1	−1.4	0.2
2	492	4	8.3	−1.5	0.1	491	9	7.5	0.5	0.6
3	491	16	10.2	1.8	0.1	490	12	9.6	0.8	0.4
4	490	17	12.4	1.3	0.2	492	17	12.0	1.5	0.1
5	492	18	14.9	0.8	0.4	491	16	14.5	0.4	0.7
6	491	15	17.9	−0.7	0.5	491	14	17.7	−0.9	0.4
7	491	17	21.3	−0.9	0.4	491	16	21.4	−1.2	0.2
8	492	24	25.9	−0.4	0.7	492	22	26.2	−0.8	0.4
9	490	31	32.9	−0.3	0.7	491	38	34.0	0.7	0.5
10	492	61	57.4	0.5	0.6	491	61	59.1	0.3	0.8

* Centre and race are also included in each of the prediction models