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Association Between Retinopathy and Cardiovascular Disease in Patients with Chronic Kidney Disease (From the Chronic Renal Insufficiency Cohort [CRIC] Study)

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Abstract

Patients with chronic kidney disease (CKD) experience co-morbid illnesses including cardiovascular disease (CVD) and retinopathy. The purpose of this study was to assess the association between retinopathy and self reported CVD in a subgroup of the participants of the Chronic Renal Insufficiency Cohort (CRIC) study. In this observational, ancillary investigation, 2605 CRIC participants were invited to participate in this study, and non-mydriatic fundus photographs in both eyes were obtained in 1936 subjects. Photographs were reviewed in a masked fashion at a central photograph reading center. Presence and severity of retinopathy (diabetic, hypertensive or other) and vessel diameter caliber were assessed using standard protocols by trained graders masked to information about study participants. History of self-reported cardiovascular disease was obtained using a medical history questionnaire. Kidney function measurements, traditional and non-traditional risk factors for CVD were obtained from the CRIC study. Greater severity of retinopathy was associated with higher prevalence of any cardiovascular disease and this association persisted after adjustment for traditional risk factors for CVD. Presence of vascular abnormalities usually associated with hypertension was also associated with increased prevalence of CVD. We found a direct relationship between CVD prevalence and mean venular caliber. In conclusion, presence of retinopathy was associated with CVD, suggesting that retinovascular pathology may be indicative of macrovascular disease even after adjustment for renal dysfunction and traditional CVD risk factors. This would make assessment of retinal morphology a valuable tool in chronic kidney disease studies of CVD outcomes.

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Keywords

Retinopathy; chronic kidney disease; cardiovascular disease

Introduction

We have conducted a study entitled Retinopathy in Chronic Renal Insufficiency (RCRIC) to investigate the association between retinopathy and cardiovascular disease (CVD) in a group of patients with chronic kidney disease (CKD) enrolled in the Chronic Renal Insufficiency Cohort (CRIC) study (1,2). We previously reported that nearly one-half of RCRIC study participants had fundus pathology that was strongly associated with risk factors for CKD (3). We now report on the presence and severity of a variety of retinopathy features, including measurements of retinal vascular calibers, and their association with self reported CVD.

Methods

The design of the CRIC study has been reported previously (1, 2). Participants for our RCRIC study were recruited at 6 of the 7 CRIC clinical centers. All 2605 CRIC participants from these 6 sites were offered participation in our RCRIC investigation. From June 2006 to May 2008, 1936 RCRIC participants were photographed. The study was approved by the Institutional Review Boards of the participating institutions. Participants provided written consent.

Trained non-ophthalmic personnel took the photographs. Participants were seated in a darkened room for five minutes to induce a physiologic, non-pharmacologic dilatation of the pupils. A Canon CR-DGI, Non-Mydriatic Retinal Camera (Canon Inc, Tokyo Japan) was used to obtain 45 degree digital, color fundus photographs. A set of two images, one centered on the macula and the other on the optic disc, was obtained from each eye. A participant was considered eligible for analysis if either the disc or macula photographs of one eye could be evaluated.

Digital fundus photographs were assessed by trained graders and a retinal specialist at the RCRIC Fundus Photograph Reading Center at the University of Pennsylvania. Readers were masked to participant's clinical and demographic information. Fundus pathology including retinopathy (diabetic, hypertensive, or other) and measurement of the diameter of the major retinal vessels were assessed. Because the readers were unaware of the diabetic or hypertensive status of the participants, retinopathy was evaluated without assumption of cause.

The Atherosclerosis Risk in Communities (ARIC) fundus photographic (4) and the Early Treatment of Diabetic Retinopathy (ETDRS) grading protocols (5) were used to grade retinopathy due to diabetes mellitus, systemic hypertension, and other conditions. The Multi-Ethnic Study of Artherosclerosis (MESA) protocol was used for the evaluation of macular edema (6). These grading protocols have been previously validated in diabetic and non-diabetic populations. Evaluations of digital photographs were done on color calibrated monitors by a single masked reader using standard protocols with standardized photographic field definitions.

Retinal abnormalities were graded by referring to standard photographs: microaneurysms, retinal hemorrhages, hemorrhages and/or microaneurysms, retinal hemorrhage type (flame or blot), drusen, hard exudates, cotton-wool patches or soft exudates, intraretinal

microvascular abnormalities, new vessels on or within 1 disc diameters of the disc or elsewhere, fibrous proliferation, and scars from previous pan retinal photocoagulation.

An EDTRS severity score was assigned for each eye (5). The score is on an ordinal scale and is not a continuous variable. Scores were classified as normal (<14), very mild non proliferative retinopathy (14 to 20), non-proliferative retinopathy (35 to 53); and proliferative retinopathy (>60). The score of the eye with more advanced retinopathy was used as the score of the participant; when only one eye was available that score was used. A total of 116 participants (6%) had photographs that could not be graded for both eyes. Among them, 38 participants had photographs in which no features could be detected. The remaining 78 participants had photographs that were blurry or dark, and although some mild retinopathy features were present, an accurate grading could not be assigned because more advanced and subtle retinopathy features were not discernible.

Grade re-grade reliability was assessed in 200 participants. Weighted Kappa for participant's ETDRS score was 0.77 (95% CI: 0.67-0.88), a value consistent with the reproducibility assessment reported by the ETDRS study (5).

Image processor measurements of vascular arteriolar and venular calibers were performed according to the ARIC protocol, using IVAN (interactive vessel analysis) software developed at the University of Wisconsin (4). Graders overlaid a grid centered on the disc to establish the distance from the optic nerve. Vessels were measured within an annulus spanning 0.5 to 1 disc diameter from the edge of the disc. Graders identified major arterioles and venules and chose segments most suitable for measurement according to the vessel's sharpness and straightness. The diameter of up to 6 arterioles and 6 venules were averaged (4).

Identification of clinical cardiovascular outcomes was carried out by the CRIC clinical centers. At baseline, and then every 6 months, patients were queried through a questionnaire about possible cardiovascular hospitalizations and outpatient cardiovascular tests and interventions. Cardiovascular events such as myocardial infarction and/or revascularization procedures, stroke, new onset or worsening of congestive heart failure, abnormal heart rhythm and peripheral arterial disease were identified.

We compared baseline characteristics of participants with and without gradable photographs. We used t-tests for continuous variables and Fisher's exact tests for categorical variables. Participant with ungradable photographs were included in a separate retinopathy category and the analysis did not assume ordering among the categories. We performed two separate analyses of the relationship between retinopathy and CVD, one included and the other excluded the ungradable category.

The relationship between fundus features and CVD was assessed by odd ratio (OR) and their 95% confidence intervals obtained from univariate and multivariate logistic regression models. The multivariate models were adjusted by traditional risk factors for CVD including age, sex, systolic blood pressure, smoking status (never/former/current), diabetes, hypertension, low density lipoprotein, high density lipoprotein, triglycerides, hemoglobin A1C, eGFR and 24 hour urine protein. Data values from the annual visit closest in time to fundus photography were used.

For the association between vascular diameter and CVD, the averages of the vascular diameters from both eyes were calculated for each person. When measurements were available for only one eye, that measurement was used for the person. Diameter measurements were divided into quartiles due to non-monotonic relationships between vascular diameters and CVD. The comparison of CVD among 4 quartiles was assessed by

univariate logistic regression models and multivariate logistic regression models adjusted by traditional risk factors listed above.

The above analyses were performed for each type-specific CVD including: myocardial infarction and/or prior revascularization, atrial fibrillation or heart arrhythmia, congestive heart failure, peripheral arterial disease, and stroke. The same analysis was performed for any CVD, which was defined as the presence of any of these type-specific CVDs, excluding atrial fibrillation or heart arrhythmia. For the association between retinopathy or vessel calibers and any CVD, a separately analyses was also performed for diabetic participants and non-diabetic participants. All data analyses were performed in SAS v9.2 (SAS Institute Inc., Cary, NC), and two-sided p-value <0.05 was considered to be statistically significant.

We used the CRIC definitions of diabetes mellitus and systemic hypertension (1, 2). Estimated glomerular filtration rate (eGFR) was calculated using the Modification in Diet in Renal Disease equation (1, 2, 7).

Results

A total of 1936 of 2605 (74%) eligible participants were photographed. Their baseline clinical and demographic characteristics have been described in a previous report (3). Mean systolic blood pressure and body mass index, prevalence of diabetes, and proportion of women were significantly lower, and mean eGFR was significantly higher in participants that had photographs, indicating that the photographed group was healthier than the group not photographed (3).

Among the 1936 participants with baseline photographs, 1820 (94.0%) had photos that were of sufficient quality to allow retinopathy scoring, and 1599 (82.6%) had photographs that allowed retinal vessel caliber measurements in at least one eye. In comparison to the 1820 participants that had gradable photographs, the 116 participants that had ungradable photographs were older, had significantly lower average eGFR, and had higher systolic blood pressure, urine protein, hemoglobin A1C, and low density lipoprotein. They also had higher prevalence of diabetes and hypertension (Table 1).

Retinopathy was present in 456 (49%) of 925 participants with diabetes and in 115 (11%) of 1011 participants without diabetes ($p<0.001$). Among 1714 participants with hypertension 548 (32%) had retinopathy, whereas among 221 participants without hypertension, 22 (10%) had retinopathy ($p<0.001$). There were 182 participants with neither diabetes mellitus nor hypertension and 4 (2%) had mild retinopathy

Retinopathy was associated with increased prevalence of any CVD in the univariate analysis ($p<0.001$; Table 2). This significant relationship persisted after adjustment for other CVD risk factors (multivariate analysis, $p<0.01$). However, the risk of any CVD did not increase as severity of retinopathy increased. Interestingly, participants with ungradable photographs had the highest risk of any CVD (Table 2). Among persons with diabetes, a similar relationship was observed ($p<0.01$; Table 2), and mild retinopathy was associated with the highest risk of any CVD.

We used a stepwise selection method for logistic regression to identify the retinopathy features independently associated with any CVD. Only fibrous proliferation ($p=0.03$), a feature included in the EDTRS grading, and arteriovenous abnormalities ($p=0.02$), a feature commonly associated with systemic hypertension, were statistically significantly associated with increased risk of any CVD.

We investigated whether there was an interaction between eGFR and retinopathy or proteinuria and retinopathy with any CVD. We found no statistically significant modulating effect of eGFR or proteinuria on this relationship (data not shown).

We found no associations between arterial diameter and presence of any CVD. A significant association was detected, however, between venous diameter and any CVD (univariate linear trend analysis, $p=0.02$, Table 3). Larger venous diameter was associated with an increased risk of any CVD and this association remained after adjustment for CVD risk factors (linear trend $p=0.01$). Among participants with diabetes this relationship was not statistically significant ($p=0.10$; Table 3).

The strongest associations between retinopathy and specific cardiovascular diseases were observed for myocardial infarction (MI) and/or revascularization and stroke (Table 4). A significant association was detected between retinopathy level and history of MI and/or prior revascularization (univariate analysis, $p<0.001$; multivariate analysis, $p=0.02$). Interestingly, mild non proliferative retinopathy showed the strongest relationship with MI and/or revascularization (odds ratio 1.93, 95% confidence interval 1.27-2.94, Table 5). The association between greater retinal venous diameter and MI was not significant in the univariate analysis ($p=0.13$) but was in the multivariate analysis ($p=0.03$, Table 5).

Retinopathy level was associated with history of atrial fibrillation or heart arrhythmia (Table 4; univariate analysis $p=0.045$), but the association weakened after adjustment for risk factors (multivariate analysis $p=0.09$, Table 4). There was no evidence of increasing risk with more retinopathy, and therefore, whether there is a relationship is unclear. No significant relationship between vessel diameter and arrhythmia was detected (Table 5).

Retinopathy was associated with congestive heart failure (CHF, univariate analysis, $p<0.001$) but this relationship weakened after adjustment for CVD risk factors (multivariate analysis, $p=0.08$, Table 4). Although the overall relationship was marginal, for the highest level of retinopathy the odds ratio was statistically significant (OR 1.98 [95% CI 1.17 - 3.35, $p=0.01$]). Larger venous diameter was associated with increased risk of CHF (univariate analysis, $p<0.001$; Table 5), and the relationship remained significant after adjustment of risk factors (multivariate analysis $p=0.009$).

Retinopathy was associated with peripheral arterial disease (PAD) on a univariate analysis ($p<0.001$, Table 4), but this relationship weakened considerably after adjustment for risk factors (multivariate analysis, $p=0.45$). Larger venules were associated with higher PAD risk (univariate analysis, $p=0.03$) but the association weakened after multivariate adjustment for risk factors ($p=0.19$, Table 5).

Finally, retinopathy was associated with stroke (univariate analysis, $p<0.001$). This relationship remained significant after adjustment for risk factors (multivariate analysis, $p<0.01$, Table 4). Larger veins were associated with higher risk of stroke (univariate analysis, $p=0.046$) and the association remained significant after multivariate adjustment for risk factors (multivariate analysis, $p=0.04$).

Discussion

This is the first comprehensive study of retinal pathology among subjects with CKD over a wide range of kidney function. Our findings show significant associations between retinopathy level and a number of cardiovascular conditions. Many of these associations persist after adjustment for potent traditional CVD risk factors, indicating that presence of retinopathy may provide additional information on CVD.

Individual retinopathy features develop through different mechanisms. To gain additional insight into the possible common pathologic mechanisms between retinopathy and CVD, we investigated the association of each individual retinopathy feature and CVD.

For example, microaneurysms are saccular dilatations of the microvasculature often associated with increased basement membrane thickness and loss of pericytes that mediate vasomotion and vascular permeability (8). Retinal hard exudates and hemorrhages, on the other hand, result from increased permeability that may be related to this loss of pericytes, among others. Soft exudates or cotton wool spots are micro-infarcts produced by occlusion of the microvasculature. Neovascularization and intraretinal microvascular abnormalities, an incipient form of neovascularization, are usually caused by retinal ischemia and hypoxia leading to the proliferation of vascular endothelial cells (8) that eventually causes fibrous proliferation. All these pathologic features are associated with endothelial dysfunction, and inflammatory processes (9, 10) leading to circulatory abnormalities and reduced vascular reactivity (11, 12) that may occur throughout the body leading to common pathologic changes that may affect the retina and the kidney and heart (13).

Among all the individual retinopathy features assessed, the association with any CVD was mostly driven by: a) fibrous proliferation, a feature of advanced retinopathy that hints at an etiologic role for hypoxia/ischemia; and b) arteriovenous abnormalities, a vascular pathologic change associated with hypertension. These results suggest that hypoxia/ischemia and hypertension may have an important etiologic role in the association between retinopathy and any CVD.

Systemic hypertension and diabetes mellitus are important risk factors for the development of both retinopathy and CVD. Histopathology studies have shown that these retinopathy characteristics reflect microvascular damage produced by aging, hypertension and other processes (14-16). Several pathological studies have suggested that retinal microvascular changes are associated with vascular abnormalities in other parts of the body. In response to hypertension, for example, the retinal arterioles narrow and the media becomes thickened and sclerotic (15). Similar changes have been observed in myocardial arterioles (17, 18) and kidney arterioles (6) in systemic hypertension.

A previous population based cohort study (19) has shown strong associations between retinal findings and systemic conditions. Retinal vascular abnormalities were associated with higher blood pressure (20-22) and markers of inflammation (23) and endothelial dysfunction (10), suggesting that these retinal abnormalities could be useful indicators of cumulative microvascular damage from hypertension, inflammation, diabetes and other processes (10, 24).

We show an association between retinal venular caliber and any CVD. Participants with the largest quartile of venous diameter had a significantly higher risk of any CVD, even after adjustment for other risk factors. Similar relationships were also observed in our study between retinal venular caliber and CHF and stroke. Retinal venular dilatation has been associated with poor glycemic control (25), obesity, inflammation, endothelial dysfunction (10), progression of diabetic retinopathy (26) and genetic markers (27), and these conditions may play a role in the development of CVD. Our results in this cohort of patients with kidney disease are consistent with other population based studies showing associations between larger retinal venous diameter and coronary heart disease and stroke (28, 29). A different recent report, however, did not detect any significant association between retinal vascular diameter and the development of CKD (30).

A limitation of our study is the self reporting nature of our CVD data, and the fact that some participants had photographs that were ungradable. Interestingly, ungradable photographs

were associated with higher odds ratios for CVD. Ungradable photographs may be caused by decreased media clarity caused by cataracts, vitreous hemorrhage, retinal detachment, and fixed pupils. In addition, patients that are sicker may not maintain fixation for repeated photography. A previous study also reported that eyes with ungradable photographs tend to have increased eye pathology (4) suggesting that our study may underestimate the amount and severity of eye pathology in the population studied.

Our study demonstrates a strong association between the presence of retinopathy and CVD in patients with kidney disease, supporting the hypothesis that retinovascular pathology may reflect cardiovascular and renal vascular pathology. Our results also highlight the usefulness of an eye evaluation in the assessment of CVD in these patients.

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Table 1

Comparison of baseline characteristics between patients with and without gradable photos

Variable	With gradable photo n=1820 (94%)	Without gradable photo n=116 (6%)	p-value*
n (%)			
Female	825 (45.3%)	56 (48.3%)	0.56
Non-smoker	839 (46.1%)	42 (36.2%)	
Former smoker	765 (42.0%)	58 (50.0%)	0.11
Current smoker	216 (11.9%)	16 (13.8%)	
Diabetes mellitus	845 (46.4%)	80 (69.0%)	<0.001
Hypertension	1603 (88.1%)	111 (95.7%)	<0.01
Any Cardio-Vascular Disease	625 (34.3%)	66 (56.9%)	<0.001
Mean (SD)			
Age (years)	60.0 (10.9)	64.3 (9.2)	<0.001
Systolic Blood Pressure (mmHg)	126.5 (21.5)	134.4 (23.6)	<0.001
High-density Lipoprotein (mg/dL)	48.7 (15.8)	48.6 (14.9)	0.97
Low-density Lipoprotein (mg/dL)	99.1 (33.5)	91.9 (31.6)	0.03
Triglycerides (mg/dL)	147.9 (102.3)	144.1 (114.2)	0.70
Hemoglobin A1C (%)	6.48 (1.43)	7.11 (1.49)	<0.001
eGFR (mL/min/1.73m ²)	41.7 (16.0)	36.0 (15.1)	<0.001
Median (25% - 75%)			
Urine Protein (g/24H)	0.16 (0.06 - 0.80)	0.25 (0.09 - 1.42)	0.02

SD = Standard deviation. eGFR= Estimated glomerular filtration rate

* P-value for comparisons calculated by Fisher exact test for categorical variables and two sample t-test for continuous variables.

Table 2

The association of retinal level with any cardiovascular disease

		Univariate			Multivariate *	
	n	Any CVD (%)	OR (95% CI)	p-value	OR (95% CI)	p-value
Retinal Level [§] , All participants						
No NPR	1249	353 (28.3%)	1.00	<0.001 [‡]	1.00	<0.01 [‡]
Mild NPR	142	65 (45.8%)	2.14 (1.51 - 3.05)		1.79 (1.21 - 2.66)	
NPR	243	108 (44.4%)	2.03 (1.53 - 2.69)		1.22 (0.86 - 1.74)	
PR	186	99 (53.2%)	2.89 (2.11 - 3.95)		1.76 (1.17 - 2.63)	
Ungradable	116	66 (56.9%)	3.35 (2.27 - 4.94)	<0.001 [‡]	1.93 (1.24 - 2.99)	<0.01 [‡]
Retinal Level [§] , Diabetic patients						
No NPR	389	152 (39.1%)	1.00	<0.001 [‡]	1.00	<0.01 [‡]
Mild NPR	67	39 (58.2%)	2.17 (1.28 - 3.68)		2.35 (1.33 - 4.15)	
NPR	214	99 (46.3%)	1.34 (0.96 - 1.88)		1.34 (0.91 - 1.98)	
PR	175	95 (54.3%)	1.85 (1.29 - 2.66)		1.88 (1.21 - 2.92)	
Ungradable	80	46 (57.5%)	2.11 (1.30 - 3.44)	<0.001 [‡]	1.82 (1.07 - 3.10)	<0.01 [‡]
Retinal Level [§] , Non-Diabetic patients						
No NPR	860	201 (23.4%)	1.00	0.12 [‡]	1.00	0.70 [‡]
Mild NPR	75	26 (34.7%)	1.74 (1.05 - 2.87)		1.33 (0.75 - 2.34)	
NPR	29	9 (31.0%)	1.48 (0.66 - 3.29)		0.99 (0.40 - 2.42)	
PR	11	4 (36.4%)	1.87 (0.54 - 6.46)		1.73 (0.44 - 6.85)	
Ungradable	36	20 (55.6%)	4.10 (2.08 - 8.06)	<0.001 [‡]	2.55 (1.15 - 5.66)	0.17 [‡]

NPR= non-proliferative retinopathy. PR= proliferative retinopathy.

[§]Based on worst eye[‡]p-value for comparison among retinal levels excluding ungradeable[‡]p-value for comparison among all levels including ungradeable^{*} Adjusted by Age, Sex, Low-density Lipoprotein, High-density Lipoprotein, Systolic blood pressure, Smoking Status, Diabetes, Hypertension, Hemoglobin A1C, Triglycerides, eGFR, and log of 24H Urine Protein

Table 3

The association of retinal vessel caliber with any cardiovascular disease Univariate Multivariate*

Univariate				Multivariate [*]		
Retinal Vessel Caliber [§]	n	Any CVD (%)	OR (95% CI)	p-value [†]	OR (95% CI)	p-value [†]
Arteriole diameter, All patients						
1st Quartile (Lowest	399	133 (33.3%)	1.00	0.69	1.00	0.25
2nd Quartile	400	124	(31.0%)	0.90 (0.67 - 1.21)	0.82 (0.58 - 1.14)	
3rd Quartile	400	121 (30.3%)	0.87 (0.64 - 1.17)		0.90 (0.64 - 1.27)	
4th Quartile (Highest)	400	140 (35.0%)	1.08 (0.80 - 1.44)		1.19 (0.85 - 1.69)	
Vein diameter, All patients						
1st Quartile	399	129 (32.3%)	1.00	0.02	1.00	0.01
2nd Quartile	400	107 (26.8%)	0.76 (0.56 - 1.04)		0.87 (0.61 - 1.23)	
3rd Quartile	400	127 (31.8%)		0.97 (0.72 - 1.31)	1.15 (0.82 - 1.62)	
4th Quartile	400	155 (38.8%)	1.32 (0.99 - 1.77)		1.47 (1.03 - 2.08)	
Arteriole diameter, Diabetic patients						
1st Quartile	148	77 (52.0%)	1.00	0.28	1.00	0.48
2nd Quartile	167	66 (39.5%)	0.60 (0.39 - 0.94)		0.51 (0.31 - 0.84)	
3rd Quartile	163	61 (37.4%)	0.55 (0.35 - 0.87)		0.58 (0.35 - 0.96)	
4th Quartile	189	88 (46.6%)	0.80 (0.52 - 1.24)		0.80 (0.49 - 1.31)	
Vein diameter, Diabetic patients						
1st Quartile	152	68 (44.7%)	1.00	0.25	1.00	0.10
2nd Quartile	139	51 (36.7%)	0.72 (0.45 - 1.15)		0.74 (0.44 - 1.23)	
3rd Quartile	176	74 (42.0%)	0.90 (0.58 - 1.39)		1.03 (0.63 - 1.66)	
4th Quartile	200	99 (49.5%)	1.21 (0.79 - 1.85)		1.38 (0.85 - 2.26)	

CVD=Cardiovascular disease. OR=Odds ratio. CI=Confidence interval.

[§]Based on mean of both eyes[†]p-value is for test of linear trend

* Adjusted by Age, Sex, Low-density Lipoprotein, High-density Lipoprotein, Systolic blood pressure, Smoking Status, Diabetes, Hypertension, Hemoglobin A1C, Triglycerides, eGFR, and log of 24H Urine Protein

Table 4

The association of retinal level with specific cardiovascular conditions

			Univariate		Multivariate*	
	n	Type-specific CVD (%)	OR (95% CI)	p-value	OR (95% CI)	p-value
Retinal Level[§], MI or prior revascularization (n=451)						
No NPR	1249	235 (18.8%)	1.00	<0.001 [†]	1.00	0.02 [†]
Mild NPR	142	47 (33.1%)	2.13 (1.46 - 3.11)		1.93 (1.27 - 2.94)	
NPR	243	67 (27.6%)	1.64 (1.20 - 2.25)		1.03 (0.70 - 1.51)	
PR	186	61 (32.8%)	2.11 (1.50 - 2.95)		1.34 (0.87 - 2.06)	
Ungradeable	116	41 (35.3%)	2.36 (1.57 - 3.54)	<0.001*	1.44 (0.91 - 2.26)	0.02*
Retinal Level[§], Atrial fibrillation or heart arrhythmia (n=366)						
No NPR	1249	213 (17.1%)	1.00	0.045 [†]	1.00	0.09 [†]
Mild NPR	142	30 (21.1%)	1.30 (0.85 - 2.00)		1.17 (0.75 - 1.83)	
NPR	243	59 (24.3%)	1.56 (1.12 - 2.17)		1.20 (0.81 - 1.76)	
PR	186	30 (16.1%)	0.94 (0.62 - 1.42)		0.64 (0.39 - 1.05)	
Ungradeable	116	34 (29.3%)	2.02 (1.32 - 3.09)	<0.01*	1.52 (0.96 - 2.40)	0.047*
Retinal Level[§], Congestive Heart Failure (n=201)						
No NPR	1249	84 (6.7%)	1.00	<0.001 [†]	1.00	0.08 [†]
Mild NPR	142	19 (13.4%)	2.14 (1.26 - 3.65)		1.36 (0.75 - 2.45)	
NPR	243	35 (14.4%)	2.33 (1.53 - 3.56)		1.25 (0.75 - 2.07)	
PR	186	42 (22.6%)	4.05 (2.69 - 6.09)		1.98 (1.17 - 3.35)	
Ungradeable	116	21 (18.1%)	3.07 (1.82 - 5.17)	<0.001*	1.58 (0.89 - 2.80)	0.17*
Retinal Level[§], Peripheral Arterial Disease (n=149)						
No NPR	1249	66 (5.3%)	1.00	<0.001 [†]	1.00	0.45 [†]
Mild NPR	142	10 (7.0%)	1.36 (0.68 - 2.70)		0.92 (0.44 - 1.95)	
NPR	243	29 (11.9%)	2.43 (1.53 - 3.85)		1.34 (0.78 - 2.32)	
PR	186	26 (14.0%)	2.91 (1.80 - 4.72)		1.55 (0.85 - 2.83)	
Ungradeable	116	18 (15.5%)	3.29 (1.88 - 5.77)	<0.001*	1.62 (0.86 - 3.03)	0.47*
Retinal Level[§], Stroke (n=202)						
No NPR	1249	101 (8.1%)	1.00	<0.001 [†]	1.00	<0.01 [†]
Mild NPR	142	19 (13.4%)	1.76 (1.04 - 2.97)		1.58 (0.92 - 2.71)	
NPR	243	29 (11.9%)	1.54 (0.99 - 2.39)		1.17 (0.69 - 1.98)	
PR	186	33 (17.7%)	2.45 (1.60 - 3.76)		2.43 (1.43 - 4.15)	
Ungradeable	116	20 (17.2%)	2.37 (1.40 - 3.99)	<0.001*	1.65 (0.93 - 2.93)	0.01*

CVD=Cardiovascular disease. OR=Odds ratio. CI=Confidence interval. MI=Myocardial infarction. NPR= non-proliferative retinopathy. PR= proliferative retinopathy.

[§]Based on worst eye

[†] p-value for comparison among retinal levels excluding ungradeable

[‡] p-value for comparison among all levels including ungradeable

^{*} Adjusted by Age, Sex, Low-density Lipoprotein, High-density Lipoprotein, Systolic blood pressure, Smoking Status, Diabetes, Hypertension, Hemoglobin A1C, Triglycerides, eGFR, and log of 24H Urine Protein

Table 5

The association of retinal vessel caliber with specific cardiovascular conditions

			Univariate	Multivariate*		
Retinal Vessel Caliber [§]	n	Type-specific CVD (%)	OR (95% CI)	p-value [†]	OR (95% CI)	p-value [†]
Arteriole diameter, MI or prior revascularization						
1st Quartile (Lowest)	399	83 (20.8%)	1.00	0.64	1.00	0.25
2nd Quartile	400	84 (21.0%)	1.01 (0.72 - 1.42)		0.94 (0.64 - 1.37)	
3rd Quartile	400	84 (21.0%)	1.01 (0.72 - 1.42)		1.08 (0.74 - 1.59)	
4th Quartile (Highest)	400	89 (22.3%)	1.09 (0.78 - 1.53)		1.21 (0.82 - 1.78)	
Vein diameter, MI or prior revascularization						
1st Quartile	399	87 (21.8%)	1.00	0.13	1.00	0.03
2nd Quartile	400	69 (17.3%)	0.75 (0.53 - 1.06)		0.81 (0.55 - 1.21)	
3rd Quartile	400	83 (20.8%)	0.94 (0.67 - 1.32)		1.12 (0.77 - 1.63)	
4th Quartile	400	101 (25.3%)	1.21 (0.87 - 1.68)		1.40 (0.95 - 2.06)	
Arteriole diameter, Atrial fibrillation or heart arrhythmia						
1st Quartile	399	82 (20.6%)	1.00	0.79	1.00	0.43
2nd Quartile	400	65 (16.3%)	0.75 (0.52 - 1.08)		0.67 (0.46 - 0.97)	
3rd Quartile	400	65 (16.3%)	0.75 (0.52 - 1.08)		0.73 (0.50 - 1.07)	
4th Quartile	400	79 (19.8%)	0.95 (0.67 - 1.34)		0.83 (0.57 - 1.20)	
Vein diameter, Atrial fibrillation or heart arrhythmia						
1st Quartile	399	82 (20.6%)	1.00	0.69	1.00	0.54
2nd Quartile	400	61 (15.3%)	0.70 (0.48 - 1.00)		0.66 (0.45 - 0.97)	
3rd Quartile	400	76 (19.0%)	0.91 (0.64 - 1.28)		0.88 (0.61 - 1.27)	
4th Quartile	400	72 (18.0%)	0.85 (0.60 - 1.21)		0.80 (0.54 - 1.18)	
Arteriole diameter, Congestive Heart Failure						
1st Quartile	399	33 (8.3%)	1.00	0.18	1.00	0.36
2nd Quartile	400	30 (7.5%)	0.90 (0.54 - 1.51)		0.75 (0.43 - 1.32)	
3rd Quartile	400	28 (7.0%)	0.83 (0.49 - 1.41)		0.79 (0.45 - 1.38)	
4th Quartile	400	46 (11.5%)	1.44 (0.90 - 2.31)		1.28 (0.76 - 2.16)	
Vein diameter, Congestive Heart Failure						
1st Quartile	399	28 (7.0%)	1.00	<0.001	1.00	<0.01
2nd Quartile	400	22 (5.5%)	0.77 (0.43 - 1.37)		0.85 (0.46 - 1.58)	
3rd Quartile	400	32 (8.0%)	1.15 (0.68 - 1.95)		1.16 (0.66 - 2.03)	
4th Quartile	400	55 (13.8%)	2.11 (1.31 - 3.41)		1.92 (1.12 - 3.30)	
Arteriole diameter, Peripheral Arterial Disease						
1st Quartile	399	27 (6.8%)	1.00	0.13	1.00	0.06
2nd Quartile	400	16 (4.0%)	0.57 (0.30 - 1.08)		0.61 (0.30 - 1.22)	
3rd Quartile	400	23 (5.8%)	0.84 (0.47 - 1.49)		0.99 (0.52 - 1.89)	
4th Quartile	400	36 (9.0%)	1.36 (0.81 - 2.29)		1.58 (0.86 - 2.88)	

			Univariate		Multivariate*	
Retinal Vessel Caliber [§]	n	Type-specific CVD (%)	OR (95% CI)	p-value [†]	OR (95% CI)	p-value [†]
Vein diameter, Peripheral Arterial Disease						
1st Quartile	399	24 (6.0%)	1.00	0.03	1.00	0.19
2nd Quartile	400	17 (4.3%)	0.69 (0.37 - 1.31)		0.73 (0.36 - 1.47)	
3rd Quartile	400	22 (5.5%)	0.91 (0.50 - 1.65)		0.92 (0.48 - 1.75)	
4th Quartile	400	39 (9.8%)	1.69 (0.99 - 2.86)		1.44 (0.78 - 2.65)	
Arteriole diameter, Stroke						
1st Quartile	399	38 (9.5%)	1.00	0.74	1.00	0.48
2nd Quartile	400	36 (9.0%)	0.94 (0.58 - 1.52)		0.97 (0.59 - 1.61)	
3rd Quartile	400	39 (9.8%)	1.03 (0.64 - 1.64)		1.08 (0.65 - 1.80)	
4th Quartile	400	40 (10.0%)	1.06 (0.66 - 1.68)		1.17 (0.70 - 1.94)	
Vein diameter, Stroke						
1st Quartile	399	32 (8.0%)	1.00	0.046	1.00	0.04
2nd Quartile	400	33 (8.3%)	1.03 (0.62 - 1.71)		1.11 (0.64 - 1.92)	
3rd Quartile	400	41 (10.3%)	1.31 (0.81 - 2.13)		1.53 (0.91 - 2.57)	
4th Quartile	400	47 (11.8%)	1.53 (0.95 - 2.45)		1.59 (0.93 - 2.72)	

CVD=Cardiovascular disease. OR=Odds ratio. CI=Confidence interval. MI=Myocardial infarction.

[§]Based on mean of both eyes

[†]p-value is for test of linear trend

* Adjusted by Age, Sex, Low-density Lipoprotein, High-density Lipoprotein, Systolic blood pressure, Smoking Status, Diabetes, Hypertension, Hemoglobin A1C, Triglycerides, eGFR, and log of 24H Urine Protein