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Retinal vessel diameter and the incidence of coronary artery disease in type 1 diabetes

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Abstract

Purpose—To examine the relationship between retinal vessel diameter and coronary artery disease (CAD) incidence in type 1 diabetes (T1D) using data from the Pittsburgh Epidemiology of Diabetes Complications (EDC) Study.

Design—Prospective cohort study of childhood-onset T1D.

Methods—Data are from 448 participants who had retinal photographs taken at baseline examination (1986–1988) and no history of laser photocoagulation. Computer-assisted grading was used to measure retinal arteriolar and venular caliber. CAD incidence (CAD death, myocardial infarction, revascularization/stenosis $\geq 50\%$, ischemic ECG, or physician-diagnosed angina) was ascertained over a median follow-up time of 18 years (range: 2 months–20.5 years).

Results—Mean baseline arteriolar and venular caliber were 180.0 μm (sd=15.2) and 273.3 μm (sd=28.0), respectively; 80 (17.9%) CAD events occurred during follow-up. After covariate adjustment, for T1D duration, sex, hypertension, serum lipids, and smoking status, smaller arteriolar caliber was significantly associated with CAD (HR=1.42, $p=0.03$), but larger venular caliber was not. A vessel diameter-sex interaction term was significant for arteriolar caliber ($p=0.006$). Stratified by sex, smaller arteriolar caliber was significantly associated with the incidence of CAD in women (HR=1.92, $p=0.004$), but not men. Venular caliber was not associated with CAD in either sex.

Conclusion—Smaller arteriolar caliber may indicate an increased risk of CAD in women, but not men, with T1D. Additional studies are needed to further examine the role of microvascular disease in the pathogenesis of CAD in women with T1D.

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Introduction

Retinal vessel diameter has been shown to be associated with cardiovascular disease (CVD) and holds promise as a noninvasive technique for assessing the risk of developing coronary artery disease (CAD) in the general population.^{1–12} It has not, however, been extensively studied in persons with diabetes.^{13–18} In analyses of the study participants with type 1 diabetes (T1D) in the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR), retinal vessel diameter was found to be associated with prevalent CVD.¹⁴ Retinal vessel diameter was also related to an increased risk of angina, stroke, and cardiovascular-related death, and showed a statistically significant association with myocardial infarction (MI). However, this relationship was no longer significant after accounting for nephropathy.¹⁵ In analyses of the WESDR participants with type 2 diabetes, retinal vessel diameter was associated with risk of stroke mortality and lower extremity amputation, but was not associated with mortality due to ischemic heart disease.¹⁸ Though studies of the general population have revealed sex differences in the relationship between vessel diameter and CVD,^{1,5} it is unclear whether these are seen in T1D, where cardiovascular risk is similar by sex.^{19–24}

Retinopathy has previously been shown to be associated with the incidence of CAD in the Pittsburgh Epidemiology of Diabetes Complications (EDC) Study of T1D¹⁹, but it is unknown whether retinal vessel diameter is similarly predictive. Therefore, the purpose of this study is to examine the relationship between central retinal arteriolar and venular diameter and CAD incidence in T1D using data from the Pittsburgh EDC Study.

Methods

Study Population

All participants were identified from the Pittsburgh Epidemiology of Diabetes Complications (EDC) Study, a prospective study of childhood-onset (<18 years old at diagnosis) T1D. The participants were diagnosed with T1D or seen within one year of diagnosis at Children's Hospital of Pittsburgh between 1950 and 1980. A total of 658 individuals met the eligibility criteria and participated in the EDC baseline examination, conducted between 1986 and 1988, and participants were assessed biennially thereafter. The current analyses were performed on the 448 (68.1%) study participants for whom both central retinal arteriolar and venular equivalents were measured, and who also had no prior history of laser photocoagulation (which has been shown to decrease vessel diameters²⁵) or CAD. The 448 participants included in these analyses were somewhat younger, had shorter duration of diabetes, and lower blood pressure levels, but had no difference in sex distribution, proportion of smokers, body mass index (BMI), or glycemic control compared to those who were excluded (data not shown).

Measurement of Retinal Vessel Caliber

Measurement of retinal vascular caliber and grading of diabetic retinopathy was performed on 30° stereoscopic color fundus photographs of 3 standard fields, 1, 2, and 4 with a Zeiss camera, taken after pupil dilation. Retinal vessel calibers were measured at the Ocular Epidemiology Reading Center at the University of Wisconsin, Madison, using a standardized protocol that has been previously described.^{26–29} Information concerning reliability of grading of retinal vascular caliber at the Ocular Epidemiology Reading Center can be found in Hubbard *et al.*²⁸ After converting retinal photographs of field 1 to digital images, all arterioles and venules were measured in the area between 0.5 and 1 disc diameters (DD) from the optic disc margin using a computer-assisted program. Computer-assisted measurements of individual arterioles and venules were each combined according to formulas developed by Parr and Spears,^{26,27} Hubbard *et al.*,²⁸ and Knudtson *et al.*²⁹ to provide the average caliber of retinal arterioles (central retinal arteriolar equivalent [CRAE]) and venules (central retinal venular equivalent

[CRVE]) in that eye. Ranges of the retinal arteriolar and venular caliber were 130.9 to 241.0 μm and 191.9 to 371.4 μm , respectively.

Clinical Evaluation and Outcomes

The assessment of diabetic retinopathy and macular edema at baseline and follow-up has been described in detail elsewhere³⁰ and are modifications of the Early Treatment Diabetic Retinopathy Study adaptation of the modified Airlie House classification of diabetic retinopathy.^{31, 32} Severity of retinopathy was graded and defined as an ordinal variable (level <14 (no retinopathy), levels 14–31 (minimal to mild nonproliferative diabetic retinopathy (NPDR)), levels 40–51 (moderate to severe NPRD), and level ≥ 60 (proliferative diabetic retinopathy, PDR)). Macroalbuminuria was defined as albumin excretion rate $>200\mu\text{g}/\text{min}$ in two of three timed urine collections, renal failure, or renal transplantation.

CAD was defined as CAD death, MI and/or Q-waves with Minnesota Codes 1.1 or 1.2, stenosis $>50\%$ or revascularization, ischemic ECG (Minnesota Code 1.3, 4.1–4.3, 5.1–5.3, 7.1), or EDC physician diagnosed angina. Events were confirmed by medical records and verified by an EDC study physician masked to retinal vessel measurements.

Participants completed questionnaires concerning demographic and medical history information. Weight was measured using a balanced-beam scale with clothing during the clinical examination. Height was measured using the clinic stadiometer, with the Frankfort plane held horizontal. BMI was calculated as weight in kilograms divided by height in meters squared. Waist circumference was measured twice at the midpoint between the highest point of the iliac crest and the lowest part of the costal margin in the midaxillary line. If the two measurements differed by >0.5 cm, a third measurement was performed. The mean of the waist measurements was recorded as waist circumference. Hip girth measurement was performed at the widest point of the glutei, usually at the level of the greater femoral trochanter, and the mean of two measures was recorded as the hip circumference, in the same manner as the waist measurements. The ratio of the waist circumference to the hip circumference (WHR) was used in analyses. Stable HbA_{1c} was measured by ion-exchange chromatography (Isolab, Akron, OH). Serum total cholesterol and triglycerides were determined enzymatically.^{33, 34} HDL-cholesterol was determined using a precipitation technique with a modification³⁵ of the Lipid Research Clinics method³⁶ and LDL-cholesterol levels were calculated from the measurements of total cholesterol, triglycerides and HDL-cholesterol using the Friedwald equation.³⁷ All blood samples were taken after at least 8 hours of fasting. Three seated blood pressure readings were taken with a random-zero sphygmomanometer and the mean of the second and third readings was used in analyses, according to the Hypertension Detection and Follow-up Program Protocol.³⁸ Hypertension was defined as $>140/90$ mmHg or use of antihypertensive medication. Pulse rate was determined by palpating the radial pulse for 30 seconds and multiplying by two. White blood cell count (WBC) was obtained using a counter S-plus IV, fibrinogen was measured using the Biuret method, and serum albumin was measured using immunonephelometry.

Statistical Methods

Baseline characteristics were compared between CAD cases and noncases using Student's t-test, Wilcoxon 2-sample test for non-normally distributed variables, and chi-square test for binary variables. Age-adjusted correlations between vessel calibers and CAD risk factors were assessed using Pearson partial correlations or Spearman partial correlations, when variables were not normally distributed. Cox proportional hazard models were used to estimate the relative risk of CAD associated with a 1-standard deviation decrease in retinal arteriolar caliber and 1-standard deviation increase in venular caliber. Follow-up time was defined as the time from the baseline examination to the date of the first CAD event. For noncases, follow-up

continued until death, last contact, or censoring on November 30, 2007. The proportional hazards assumption was assessed visually by plotting the log cumulative hazard function of CAD by retinal vessel caliber and verified by showing that time-dependent vessel caliber interaction variables were not statistically significant. Arteriolar and venular calibers were included simultaneously in Cox models, as this method has been shown by Liew *et al.*³⁹ to account for correlation between the two measures, provide less biased results than separate models, and to provide more information than models using the arteriolar-to-venular ratio (AVR). Models were also re-examined separately for each retinal vessel caliber. Adjusted regression models were built using forward selection. Because age and duration of diabetes are highly correlated in this cohort ($r=0.85$), only duration was made available to multivariate models. Analyses were also stratified by sex. Alternative models examining a more strict definition for CAD were also fit, where only CAD death, MI, stenosis $>50\%$ or revascularization were considered to be CAD events. All analyses were performed using SAS 9.1.3 (SAS Institute Inc., Cary, NC).

Results

Baseline characteristics of incident CAD cases ($n=80$) and noncases ($n=368$) are shown in Table 1. The frequency of each type of first CAD event were as follows: 3 fatal MI or CAD death, 18 non-fatal MI, 27 revascularization procedures/ $\geq 50\%$ stenosis, 10 ischemic ECG, and 22 angina. Participants who went on to develop CAD had smaller mean baseline retinal arteriolar caliber as compared to noncases ($p=0.001$), but had no significant difference in CRVE ($p=0.17$). The median follow-up time was 18 years (range: 2 months – 20.5 years).

The two measures of vessel diameter were significantly correlated with one another (age-adjusted partial $r=0.54$, $p<.0001$). There were also statistically significant univariate inverse age-adjusted partial correlations (Table 2) between retinal arteriolar caliber and T1D duration, HbA1, systolic blood pressure (SBP), hypertension, blood pressure medication use, macroalbuminuria, and natural log-transformed albumin excretion rate ($\ln(\text{AER})$), but no correlation with lipid or inflammatory measures. In contrast, larger venular caliber was statistically significantly and positively associated with the entire lipid profile (except serum HDL-C), WBC, WHR, BMI, being a current or ex-smoker, severity of retinopathy, and $\ln(\text{AER})$, but not with blood pressure or hypertension. When stratified by sex (Table 2), statistically significant inverse correlations between arteriolar caliber and age, SBP, DBP, and hypertension, as well as significant, positive correlations between venular caliber and lipids (except HDL-C) and BMI, were found to occur in women only. Conversely, in men, arteriolar caliber was significantly inversely correlated with HbA1 and $\ln(\text{AER})$ and venular caliber with smoking, higher serum fibrinogen and pulse rate, and lower serum HDL-C.

In a Cox proportional hazards model including only retinal arteriolar and venular calibers as predictors, smaller arteriolar caliber was significantly associated with an increased risk of developing CAD ($\text{HR}=1.51$ per one standard deviation decrease in arteriolar caliber, $p=0.004$), while increasing venular caliber was not significantly associated ($\text{HR}=1.17$, $p=0.23$) (Table 3). Similarly, after forward selection, in a model adjusting for venular caliber, T1D duration, sex, natural log-transformed triglycerides ($\ln(\text{triglycerides})$), smoking status, and hypertension, smaller arteriolar caliber remained significantly associated with CAD risk ($\text{HR}=1.42$, $p=0.03$). An age-arteriolar caliber interaction term, added to the final model shown in Table 3, did not reach statistical significance ($p=0.10$).

Sex-specific analyses were also performed and in models adjusting only for venular caliber, as well as in multivariate models built using forward selection, smaller arteriolar caliber was significantly associated with an increased risk of CAD in women only ($p=0.0004$ and 0.004 , respectively) (Table 4). A sex by arteriolar caliber interaction term added to the final adjusted

model shown in Table 3 was statistically significant ($p=0.006$). No relationship between venular caliber and CAD was found in either sex.

Using all data, alternative models were fit separately for each vessel measurement to determine if including the two measures simultaneously, as shown above, led to any mediation of the relationship between either vessel measure and CAD. In separate, unadjusted, univariate Cox proportional hazards models, the association between retinal arteriolar caliber and CAD incidence remained significant ($p=0.007$) and venular caliber showed no association ($p=0.69$) with CAD. The covariate adjusted model reported above was also re-examined separately for each vessel measure. For arteriolar caliber (HR=1.44, 95% CI 1.10, 1.87, $p=0.01$), the results were similar to when the two vessels were modeled simultaneously. Likewise, venular caliber remained unassociated with CAD ($p=0.12$) when arteriolar caliber was not included in the same model.

Alternate models assessing risk for more strictly defined CAD (CAD death, MI, revascularization, or stenosis $>50\%$, 47 total incident events) showed a somewhat weaker association with smaller arteriolar caliber (HR=1.48, 95% CI 1.05, 2.09, $p=0.02$) than the previously described models which included ischemic ECG and angina. However, after forward selection, in a model adjusting for duration of diabetes, sex, LDL-C, ln(triglycerides), and diastolic blood pressure, arteriolar caliber was no longer significantly associated with CAD risk (HR=1.25, 95% CI 0.85, 1.86, $p=0.25$). The alternate models also showed no association with venular caliber (HR=1.25, 95% CI 0.91, 1.70, $p=0.17$), similar to the results of the models described above.

The association between arteriolar caliber and the more strictly defined CAD in women was slightly weaker than that for the more inclusive CAD outcome ($p=0.04$). A sex-arteriolar caliber interaction term was found to be statistically significant ($p=0.02$), but again was weaker than that seen when using the more broadly defined CAD. Venular caliber was not found to be associated with the more strictly defined CAD in either sex.

Discussion

The results of our study provide evidence that narrower arteriolar caliber is associated with an increased risk of coronary artery disease in women, but not men, with type 1 diabetes. This information further supports the hypothesis that microvascular changes precede macrovascular events.

Narrower arteriolar diameter was significantly correlated with measures of hypertension in women and proteinuria in men. In contrast, larger venular diameter was correlated with blood lipids, markers of inflammation, smoking, and severity of retinopathy in both sexes, as well as waist-hip ratio, BMI, and blood pressure medication use in women, but not with blood pressure itself in either sex. These results are consistent with other studies which have shown retinal arteriolar caliber to be associated with blood pressure and venular caliber to be associated with smoking, atherosclerosis, lipid levels, obesity, and inflammation.^{2,3,7-9, 40,41}

In the present study, for each standard deviation decrease in retinal arteriolar caliber there was a 42% increased risk of CAD after adjustment for other risk factors. These findings are in contrast to those reported by Alibrahim *et al.* where wider (rather than narrower) arteriolar diameter was associated with an increased risk of retinopathy in type 1 diabetes.⁴² Restricting the definition of CAD to include only the hard endpoints of CAD death, MI, stenosis $\geq 50\%$, and revascularization, showed a non-significant increase in risk of 25% per standard deviation decrease in arteriolar caliber. These results support earlier findings from analyses of type 1 diabetic participants in WESDR, where narrower arterioles were found to be associated with prevalent cardiovascular disease¹⁴ and lower arteriolar-venular ratio (AVR), which was

considered to be indicative of smaller retinal arteriolar caliber, was significantly associated with incident MI, as well as overall and CVD mortality in persons >36.2 years of age at study baseline.¹⁵

We did not find retinal venular diameter to be associated with CAD, which is in contrast to the results of the Cardiovascular Health Study (CHS)¹² and the Blue Mountains Eye Study (BMES)⁵, where larger venular diameter was found to be associated with incident coronary heart disease and cardiovascular mortality, respectively. These findings are not directly comparable, however, as both of these populations were significantly older than the EDC study population. Additionally, the results of both studies suggest that the association between venular diameter and CVD is stronger in persons with hypertension, but the prevalence of hypertension was quite low (<4%) at the EDC study baseline examination.

Interestingly, retinal arteriolar caliber was associated with incidence of CAD events in women only, a relationship which was previously shown in the Atherosclerosis Risk in Communities Study (ARIC)¹ and the Blue Mountains Eye Study, two non-T1D populations.⁵ We are unaware of previous reports of this sex-specific relationship in persons with T1D. In our study, women were at a 92% increased risk of developing CAD for each standard deviation decrease in arteriolar caliber. The reasons for this sex difference are obscure; it has been hypothesized that vascular dysfunction in the absence of obstructive coronary disease is more prevalent in women compared to men due to the influence of sex hormones.⁴³ This impaired microvascular function is thought to be a key part of the formation of atherosclerotic heart disease.⁴⁴ However, it is curious that in the EDC study, renal disease has been found to be more strongly correlated with CAD in men compared to women.¹⁹ Though we have previously shown equivalent rates of CAD in men and women, the risk factors do differ.^{19, 45}

The current study has many strengths, including its prospective design, long term follow-up (through 18 years) to detect incidence of CAD events which were verified using medical records, and masked measurement of retinal vessel diameters using standard methods. The major limitation was that participants with laser photocoagulation had to be excluded from the analyses, as the procedure is known to decrease vessel diameter.²⁵ These persons were likely the participants with the most advanced microvascular disease, so their exclusion may have introduced a selection bias where the participants at highest risk for CAD were not addressed. However, it is likely that excluding these participants actually attenuated the relationship between both retinal arteriolar and venular caliber and CAD, rather than artificially causing the results observed here. As the inclusion criteria for the study allowed for diagnosis of type 1 diabetes over 30 years (1950–1980), there is a potential for a cohort effect on the relationship between vessel diameter and CAD due to changes in the treatment of type 1 diabetes during this period. In order to assess the presence of such an effect, vessel diameter-diagnosis year interaction terms were tested, but were not found to be statistically significant (data not shown). Therefore, there is no evidence that year of diagnosis is affecting the results presented here.

In conclusion, this study has shown a sex-specific relationship between smaller retinal arteriolar caliber and the incidence of coronary artery disease in type 1 diabetes. The reason that this relationship is seen only in women remains unclear, however, these results offer further evidence to support the use of retinal vessel diameter as an early marker of CAD risk in women with type 1 diabetes.

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Table 1

Baseline characteristics of incident coronary artery disease (CAD) cases and noncases.

	CAD cases n=80	noncases n=368	p-value
Duration of Diabetes (years)	21.6 (7.5)	16.1 (6.2)	<.0001
Age (years)	30.6 (7.6)	24.3 (6.8)	<.0001
Female sex (%)	40 (50.0%)	187 (50.8%)	0.91
Retinal Arteriolar Caliber (μm)	174.9 (15.7)	181.1 (14.9)	0.001
Retinal Venular Caliber (μm)	269.4 (31.4)	274.2 (27.2)	0.17
HbA1c (%)	10.3 (1.9)	10.4 (1.8)	0.58
Total Cholesterol (mg/dl)	198.7 (35.4)	181.5 (37.4)	0.0002
HDL-Cholesterol (mg/dl)	53.4 (13.5)	55.4 (12.0)	0.20
LDL-Cholesterol (mg/dl)	121.2 (29.0)	107.5 (30.2)	0.001
Non-HDL-Cholesterol (mg/dl)	145.3 (36.5)	126.1 (36.9)	<.0001
Triglycerides (mg/dl) (median, IQ range)	82 (63–135)	75 (56–103)	0.02
White Blood Cell Count ($\times 10^3/\text{mm}^2$)	6.7 (1.9)	6.3 (1.7)	0.07
Fibrinogen (mg/dl)	292.1 (93.9)	272.0 (81.1)	0.05
Serum Albumin (mg/dl)	4.6 (0.6)	4.7 (0.63)	0.06
Pulse Rate (beats/min)	79.1 (9.0)	77.4 (9.8)	0.16
Waist-Hip Ratio	0.83 (0.07)	0.81 (0.07)	0.06
Body Mass Index (kg/m^2)	23.8 (3.3)	23.3 (3.2)	0.15
Systolic Blood Pressure (mm Hg)	113.7 (12.3)	109.2 (11.8)	0.002
Diastolic Blood Pressure (mm Hg)	73.1 (10.1)	70.0 (9.2)	0.003
Hypertension (%)	9 (11.3%)	17 (4.6%)	0.03
Blood Pressure Medication Use (%)	5 (6.4%)	5 (1.4%)	0.02
Current Smokers (%)	20 (25.0%)	67 (18.2%)	0.19
Ever Smokers (%)	37 (46.3%)	107 (29.1%)	0.004
Proliferative Retinopathy (%)	8 (10.0%)	24 (6.5%)	0.27
Macroalbuminuria (%)	17 (21.3%)	39 (10.6%)	0.01
Albumin Excretion Rate ($\mu\text{g}/\text{min}$) (median, IQ range)	15.5 (7.8–171.5)	10.5 (6.5–27.1)	0.004

Values are mean (sd) unless indicated.

Table 2
Age-adjusted correlations between vessel calibers and coronary artery disease risk factors

Risk Factor	Overall (n=448)			Male (n=221)			Female (n=227)		
	Arteriolar Caliber	Venular caliber	Arteriolar Caliber	Arteriolar Caliber	Venular caliber	Arteriolar Caliber	Arteriolar Caliber	Venular caliber	
Retinal Venular Caliber	0.54 ^{***}	-	0.59 ^{***}	0.54 ^{***}	-	0.54 ^{***}	-	-	
Duration of Diabetes (years)	-0.09 [*]	0.05	-0.08	-0.08	0.11	-0.11	-0.0002	-0.0002	
Age (years) ¹	-0.18 ^{**}	-0.08	-0.004	-0.004	-0.24 ^{**}	-0.24 ^{**}	-0.14 [*]	-0.14 [*]	
Female Sex ²	-0.05	-0.01	-	-	-	-	-	-	
HbA1 (%)	-0.10 [*]	0.05	-0.17 [*]	-0.17 [*]	0.07	-0.03	0.03	0.03	
Total Cholesterol (mg/dl)	0.001	0.11 [*]	-0.05	-0.05	0.05	0.04	0.16 [*]	0.16 [*]	
HDL-Cholesterol (mg/dl)	-0.02	-0.08	-0.06	-0.06	-0.16 [*]	0.03	0.002	0.002	
LDL-Cholesterol (mg/dl)	0.02	0.13 ^{**}	-0.02	-0.02	0.08	0.04	0.16 [*]	0.16 [*]	
Non-HDL-Cholesterol (mg/dl)	0.01	0.14 ^{**}	-0.03	-0.03	0.10	0.02	0.16 [*]	0.16 [*]	
ln(Triglycerides) (mg/dl)	-0.04	0.10	-0.02	-0.02	0.10	-0.10	0.08	0.08	
White Blood Cell Count ($\times 10^3/mm^3$)	-0.04	0.17 ^{**}	0.04	0.04	0.20 ^{**}	-0.12	0.13 [*]	0.13 [*]	
Fibrinogen (mg/dl)	-0.12	0.07	-0.09	-0.09	0.15 [*]	-0.15 [*]	0.01	0.01	
Serum Albumin (mg/dl)	0.11	0.001	0.08	0.08	-0.01	0.13	-0.01	-0.01	
Pulse Rate (beats/min)	-0.06	0.10 [*]	-0.03	-0.03	0.19 ^{**}	-0.08	0.03	0.03	
Waist-Hip Ratio	0.04	0.10 [*]	0.05	0.05	0.09	-0.001	0.12	0.12	
Body Mass Index (kg/m ²)	0.05	0.10 [*]	0.06	0.06	0.04	0.02	0.13 [*]	0.13 [*]	
Systolic Blood Pressure (mm Hg)	-0.15 ^{**}	0.02	-0.12	-0.12	-0.05	-0.20 ^{**}	0.03	0.03	
Diastolic Blood Pressure (mm Hg)	-0.08	0.06	-0.05	-0.05	0.08	-0.14 [*]	0.02	0.02	
Hypertension ²	-0.19 ^{**}	-0.07	-0.14	-0.14	-0.18	-0.25 ^{**}	0.03	0.03	
Blood Pressure Medication ²	-0.15 ^{**}	-0.12	-0.08	-0.08	-0.13	-0.22 [*]	-0.11	-0.11	
Current Smoker ²	0.06	0.22 ^{**}	0.08	0.08	0.29 ^{**}	0.03	0.16	0.16	
Ever Smoker ²	0.09	0.24 ^{***}	0.16	0.16	0.37 ^{***}	0.001	0.10	0.10	
Severity of Retinopathy ²	-0.02	0.26 ^{***}	-0.03	-0.03	0.25 ^{**}	-0.04	0.29 ^{**}	0.29 ^{**}	
Macroalbuminuria ²	-0.10 [*]	0.05	-0.06	-0.06	0.01	-0.16	0.10	0.10	

Risk Factor	Overall (n=448)		Male (n=221)		Female (n=227)	
	Arteriolar Caliber	Venular caliber	Arteriolar Caliber	Venular caliber	Arteriolar Caliber	Venular caliber
ln(Albumin Excretion Rate) (µg/min)	-0.15*	0.12*	-0.18*	0.13	-0.13	0.10

Values are Pearson partial r, unless indicated.

¹ Pearson r (unadjusted)

² Spearman partial r

* p<0.05,

** p<0.01,

*** p<0.0001

Table 3

Results of Cox Proportional Hazards Models for Risk of Coronary Artery Disease (CAD) Event (CAD death, MI, Revascularization Procedure, Stenosis>50%, Ischemic ECG, Angina)

	Model 1 Unadjusted	Model 2 Adjusted for duration of T1D	Model 3 Adjusted for duration of T1D and sex	Model 4 Covariate adjusted(final)
	Hazard Ratio (95% CI)	Hazard Ratio (95% CI)	Hazard Ratio (95% CI)	Hazard Ratio (95% CI)
Retinal Arteriolar Caliber¹	1.51 (1.14, 2.00)**	1.41 (1.06, 1.88) *	1.41 (1.05, 1.88) *	1.42 (1.04, 1.96) *
Retinal Venular Caliber	1.17 (0.91, 1.51)	1.16 (0.90, 1.50)	1.15 (0.89, 1.49)	0.98 (0.74, 1.31)
Diabetes Duration	-----	1.80 (1.46, 2.21)***	1.81 (1.47, 2.24)***	1.74 (1.39, 2.17)***
Female Sex	-----	-----	0.75 (0.47, 1.18)	0.96 (0.59, 1.56)
ln(Triglycerides)	-----	-----	-----	1.26 (1.02, 1.54) *
Smoking	-----	-----	-----	1.98 (1.15, 3.43) *
Hypertension	-----	-----	-----	2.00 (0.97, 4.12)

* p<0.05,

** p<0.01,

*** p<0.001

Results are presented as hazard ratio (HR) per 1-standard deviation increase¹ (95% confidence interval). The following covariates were also available for adjustment: HDL-C, LDL-C, pulse rate, BMI, waist-hip ratio, white blood cell count, serum albumin, fibrinogen, severity of retinopathy, and albumin excretion rate, with systolic and diastolic blood pressure, blood pressure medication use available to alternative models that did not include hypertension. Only those covariates shown in the table were included in the final model after forward selection.

¹ Hazard Ratios are per one standard deviation decrease in retinal arteriolar caliber

Table 4

Results of Cox Proportional Hazards Models for Risk of Coronary Artery Disease (CAD) Event (CAD death, MI, Revascularization Procedure, Stenosis>50%, Ischemic ECG, Angina) Stratified by Sex

	Female (n=226, 40 events)		Male (n=222, 40 events)	
	Unadjusted	Covariate Adjusted	Unadjusted	Covariate Adjusted
	Hazard Ratio (95% CI)	Hazard Ratio (95% CI)	Hazard Ratio (95% CI)	Hazard Ratio (95% CI)
Retinal Arteriolar Caliber¹	2.10 (1.39, 3.16) **	1.92 (1.24, 2.96) **	1.25 (0.83, 1.88)	1.13 (0.70, 1.81)
Retinal Venular Caliber	1.18 (0.83, 1.67)	1.18 (0.83, 1.69)	1.15 (0.78, 1.69)	0.70 (0.43, 1.16)
Diabetes Duration	-----	2.00 (1.44, 2.79) ***	-----	1.66 (1.13, 2.45) *
LDL-Cholesterol	-----	(not selected)	-----	1.40 (0.98, 1.99)
ln(Triglycerides)	-----	1.58 (1.07, 2.32) *	-----	(not selected)
Smoking	-----	(not selected)	-----	2.75 (1.27, 5.92) *
Hypertension	-----	2.79 (1.07, 7.30) *	-----	(not selected)

* p<0.05,

** p<0.01,

*** p<0.001

Results are presented as hazard ratio (HR) per 1-standard deviation increase¹ (95% confidence interval). The following covariates were also for adjustment: HDL-Cholesterol, white blood cell count, serum albumin, fibrinogen, and albumin excretion rate, with systolic and diastolic blood pressure, blood pressure medication use available to alternative models that did not include hypertension. Only those covariates shown in the table were included in the final model after forward selection.

¹ Hazard Ratios are per one standard deviation decrease in retinal arteriolar caliber