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The EYE-MI Pilot Study: A Prospective Acute Coronary Syndrome Cohort Evaluated With Retinal Optical Coherence Tomography Angiography

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Purpose. To evaluate the association between retinal microvasculature (vascular density) on optical coherence tomography-angiography (OCT-A) and the cardiovascular profile of patients hospitalized for acute coronary syndrome (ACS).

Methods. EYE-Myocardial Infarction (EYE-MI) study is a prospective cross-sectional study in the Cardiology Intensive Care Unit of Dijon University Hospital. Retinal OCT-A was performed for each patient within 2 days after admission. Superficial retinal capillary plexus (SCP) vascular density was measured. The population was divided into tertiles according to OCT-A data.

Results. Overall, 237 cases were retained for analysis. Patients in the tertile with the lowest retinal vascular density (RVD) were older, and more frequently had systemic hypertension and diabetes. Moreover, American Heart Association (AHA) risk and Global Registry of Acute Coronary Events (GRACE) scores were higher and left ventricular ejection fraction (LVEF) was lower in these patients. In multivariate analysis, the AHA risk score (odds ratio [OR], 1.06; 95% confidence interval [CI], 1.04–1.09; $P < 0.001$) and LVEF (OR, 0.95; 95% CI, 0.93–0.98; $P = 0.001$) were significantly associated with the lowest tertile of RVD. The association between RVD and a high-risk cardiovascular profile was confirmed by a moderate correlation with the GRACE scores (Spearman $r = -0.33$, $P < 0.001$).

Conclusions. SCP density measured on OCT-A was associated with the cardiovascular risk profile and with impaired LVEF in patients with a high-risk cardiovascular status. In the future, quantitative retinal microvascular data could be considered a good surrogate of the cardiovascular risk profile and could improve cardiovascular risk assessments.

Keywords: OCT-Angiography, micro-vascularization, acute coronary syndrome, AHA risk score, retinal vascular density

Microcirculation abnormalities play a key role in processes leading to the development of ischemic coronary heart disease. The quantification of microvascular perfusion is challenging, but devices are now available for clinical practice (i.e., orthogonal polarization spectral and sidestream dark-field imaging).[1,2] Unfortunately, most of time these techniques are invasive as they recommend sublingual examinations.[3] By contrast, microvascularization assessment by means of a retinal exam seems to be promising especially since retinal microvascularization could have the same physiologic and anatomic characteristics as cerebral and coronary microvascularization.[4] The semiautomatic imaging analysis software developed for these noninvasive imaging techniques provides a thorough and reproducible quantitative description of the retinal microvascular network using fundus photographs (vascular caliber, vascular tortuosity and notably the fractal dimension).[5,6] Recent studies involving large population cohorts have attempted to understand which factors contributed to the development of retinal microangiopathy and the link between retinal microangiopathy and the onset of cardiovascular events.[7–9] Retinal arteriole narrowing and retinal vein widening were shown to be associated with an increased long-term risk of death and ischemic stroke in both sexes and of coronary heart disease in women.[10,11] Moreover, from a pathophysiological point of view, an association between systemic and retinal microvasculature modifications has been described.[12,13] Retinal vascularization could thus constitute a noninvasive biomarker that provides information beyond current routine exams to evaluate systemic vascular impairment. The evaluation of retinal microvascularization was recently marked by the emergence of a new noninvasive technique: optical coherence tomography angiography (OCT-A).[14,15] OCT-A is based on blood flow imaging of the retinal and choroidal vascular network. OCT-A is used in ophthalmology to diagnose macular diseases, such as choroidal

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neovascularization in exudative age-related macular degeneration or retinal vascular occlusion. In addition, this technique allows the quantitative evaluation of vascular parameters, such as the superficial capillary plexus (SCP), the deep capillary plexus (DCP) vascular density and foveal avascular zone (FAZ) area.[16,17] However, few studies have aimed to find associations between the systemic macrovascular status and retinal microvascularization assessed by OCT-A.

Given the promising preliminary data from OCT-A studies, our hypothesis was that quantitative OCT-A microvascular data could be a surrogate of the cardiovascular risk profile. We conducted a pilot study to evaluate the association between retinal microvascular features (vascular density and FAZ area) on OCT-A and the cardiovascular profile of patients hospitalized for ACS, namely their cardiovascular risk factors, cardiovascular history and different cardiovascular scores validated for systemic cardiovascular risk profile stratification and prognosis.

Methods

Design and Population of the Study

Our study was a pilot prospective cross-sectional study conducted in the Cardiology Intensive Care Unit of Dijon University Hospital from May 9, 2016 to May 3, 2017. Patients presenting with acute coronary syndrome (ACS), with or without ST-segment elevation were included. They were taken to the ophthalmology department within the first 2 days of their hospitalization for an examination of the retinal microvasculature using OCT-A. OCT-A is a fully automated noninvasive exam. It was performed by paramedics and acquisition time lasted less than 2 minutes for each patient. The noninclusion criteria were: a preexisting retinal disease (diabetic retinopathy, vascular and degenerative macular diseases), patients under 18 years of age, those under guardianship, those without national health insurance, those who refused to take part in the study, and patients with ongoing hemodynamic instability. Severely myopic eyes were also excluded because retinal microvascular density decreases with ocular elongation (axial length greater than 26 mm).[18] The study complied with the tenets of the Declaration of Helsinki; the locally appointed ethics committee gave approval for the research protocol and written informed consent was obtained from the patient or his/her legal representative. During the OCT-A exams, a cardiologist monitored the patients' heart rhythm and hemodynamic status.

Cardiovascular Data Collection

Data were extracted from medical records and observation sheets of the Observatoire des Infarctus de Côte d'Or (RICO). The design and methods of RICO, a French regional survey for acute MI, have been detailed previously.[19] The following data were collected: age, sex, previous high blood pressure, previous diabetes, obesity (body mass index $\geq$30 kg/m^2), treated hypercholesterolemia, family history of coronary heart disease (CHD), current smoking. Cardiovascular history, a history of chronic kidney failure, vasoconstrictive drug use, hemodynamic features, and biologic parameters (creatinine, blood glucose, HbA1c, troponin, and logBNP [brain natriuretic peptide]) were also recorded. The left ventricular ejection fraction (LVEF) was measured by ultrasonography within the 24 hours following admission by an experienced operator, according to Simpson's biplane method of disks. From the above data, cardiovascular risk scores defined by the American Heart Association (AHA risk score) for a moderate-risk population were calculated. The AHA risk score was chosen as an indicator of the patients' cardiovascular risk profile because it summarizes the cardiovascular risk factors and treatments, and is associated with the onset of cardiovascular disease in the general population.[20] The AHA risk score includes age, sex, the ethnic origin, the history of arterial hypertension and diabetes, active smoking, systolic, and diastolic arterial pressure and levels of total cholesterol and HDL cholesterol.[20] The anatomic SYNTAX score, a risk stratification score for coronary lesions (length, bifurcation, diffuse disease, calcifications, thrombus, total occlusion) was determined for all of the patients who underwent coronarography.[21] We also calculated the Global Registry of Acute Cardiac Events score (GRACE) at admission to evaluate the ischemic risk for each patient and his/her prognosis by calculating in-hospital and 6-month mortality.[22] Finally, we evaluated the risk of recurrent cardiovascular events (cardiovascular death and next event within 2 years follow-up) with the Reduction of Atherothrombosis for Continued Health (REACH) score.[23] GRACE and REACH scores are prognostic and cardiovascular risk status stratification methods. They are evaluated by means of cardiovascular history, risk factors, treatment, and demographic data (see Supplementary Table for GRACE and REACH scores).

Description of Retinal Microvasculature With OCT-A

In all study participants, the OCT-A examination was performed under mydriasis obtained with eye drops containing tropicamide 0.5% (Thea, Clermont-Ferrand, France). Axial length was measured using an optical biometer (IOL Master; Carl Zeiss Meditec AG, Jena, Germany). A commercial instrument (CIRRUS HD-OCT, Model 5000; Carl Zeiss Meditec AG) was used for the OCT-A images. The technical aspects have been described recently.[24] OCT-A is a fully automated noninvasive examination. It is performed by nurses or technicians and the acquisition time is about 2 minutes for each patient. Angiography software (Angioplex, version 10; Carl Zeiss Meditec AG) was used to collect retinal vascular features in the SCP and to measure the area of the FAZ (mm^2). The SCP is the term used to refer to the vascular network from the internal limiting membrane to the inner plexiform layer of the retina. The FAZ is a retinal anatomic structure corresponding to the area of highest density of cone-type photoreceptors without capillary vascularization and it is delimited by the perifoveal anastomotic arcade (Fig. 1A). Two types of vascular density were measured: perfusion density (area, unitless), which represents the total area of perfused vasculature per unit area in a region of measurement; and vessel density (length, mm^{-1}), which represents the total length of perfused vasculature per unit area in a region of measurement. All densities were measured automatically in each sector of the SCP by the angiography software (Carl Zeiss Meditec AG; Fig. 1B). In our study, 3 $\times$ 3 mm angiograms were retained for the analysis. Quantitative studies on retinal microvasculature were shown to be repeatable.[25–27] Given the intereye symmetry ($r^2 = 0.81$, $P < 0.001$, in 114 randomly selected patients from the study cohort), the measurements were made on both eyes but one eye only was retained for the analysis according to the following procedure: (1) OCT-A of the right eye for participants born in even-numbered years and the left eye for those born in odd-numbered years, (2) in single-eye patients, the functional eye was selected, and (3) when a scan was uninterpretable for one eye, the other one was retained for the analysis. Only images with a signal strength >7/10 were retained.

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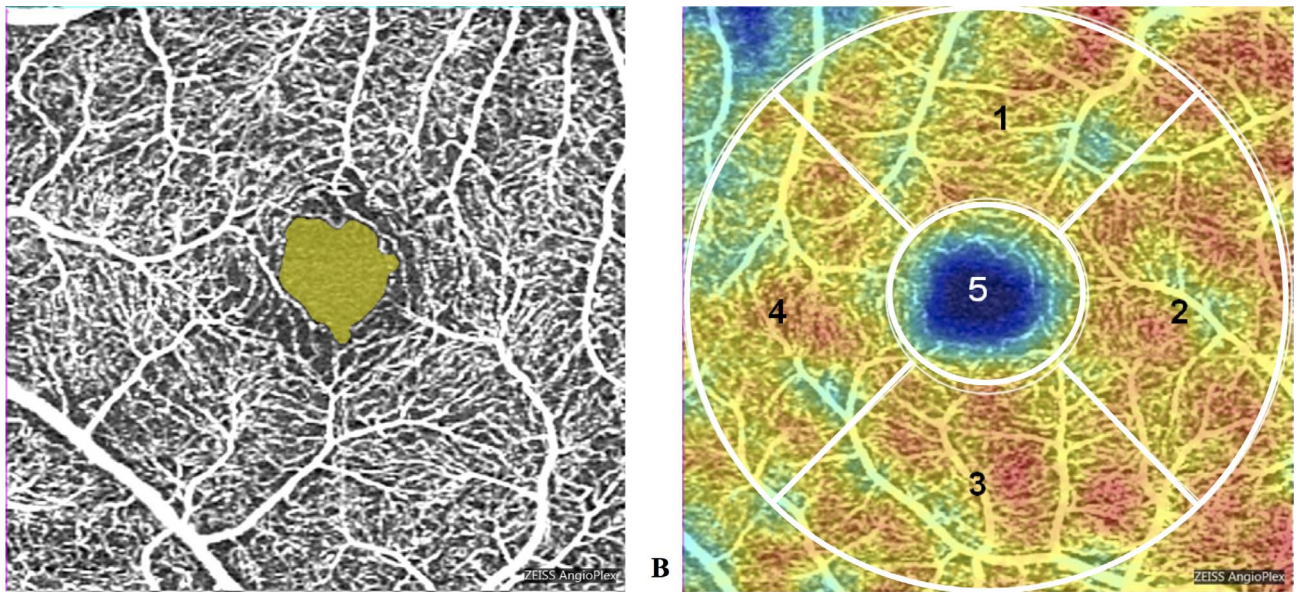

FIGURE 1. (A) Foveal avascular zone on OCT-A (Carl Zeiss Meditec AG). The area of the FAZ (*yellow*) is automatically measured by the software. (B) SCP retinal vessel density (Carl Zeiss Meditec AG). The perifoveal area was divided into five sectors; 1: superior sector, 2: nasal sector, 3: inferior sector, 4: temporal sector, 5: central sector. Inner vessel density = 1 + 2 + 3 + 4; full vessel density = 1 + 2 + 3 + 4 + 5.

Statistical Analysis

Quantitative variables are expressed as means ± standard deviations for normally distributed variables, and medians (interquartiles) for non-normally distributed variables. The normality of continuous variables was verified using the Kolmogorov-Smirnov test. Categorical variables are described as numbers (percentages). For comparisons of categoric data, a χ^2 test or Fischer's exact test was used, and for comparisons of continuous data a Mann-Whitney test was used. To find which microvascular features correlated most strongly with the patient's cardiovascular risk profile, we used Spearman's rank correlation. We undertook an evaluation of healthy volunteers (health care professionals, without any medical history nor eye disease nor cardiovascular disease) that were matched 1:1 for age and sex with patients of the EYE-Myocardial Infarction (EYE-MI) study (automatic pattern matching with SPSS version 22 software; SPSS, Inc., IBM Corp., Redmond, WA, USA). Inter and intraobserver reliability was assessed using intraclass correlation coefficients (ICC) of the absolute agreement in healthy volunteers.

A multivariate analysis (stepwise backward regression) was performed to assess which baseline parameters were independently associated with a low vascular density on OCT-A, with inclusion and exclusion thresholds of 5%. A $P < 0.05$ was considered significant statistical software (IBM Corp.) was used for the analyses.

RESULTS

Overall, 275 patients were included in the EYE-MI study and benefited from an OCT-A examination from May 9, 2016 to May 3, 2017 (Fig. 2). A total of 38 patients were excluded from the analysis because their OCT-A exams were not interpretable (Table 1). Compared with the 237 patients analyzed, these patients were significantly older (72 ± 12 vs. 62 ± 13 years, $P = 0.001$), more often had previous high blood pressure (68% vs. 51%, $P = 0.046$), previous coronary artery disease (45% vs. 22%, $P = 0.002$) and carotid atheroma (18% vs. 4%, $P = 0.001$). Table 1 shows the quantitative data for retinal microvasculature assessed using OCT-A (FAZ area and SCP vascular density). According to Spearman's rank correlation, among the features of retinal microvasculature, inner vessel density and full vessel density had the strongest correlations with AHA risk (Spearman $r = -0.540$, $P = 0.01$ and $r = -0.540$, $P = 0.01$), respectively (Table 2). As vessel density was homogeneous within each sector, and as it was more clinically relevant (it does not take into account the FAZ), inner vessel density was kept for further analysis. In the

TABLE 1. Angioplex OCT-A Analysis of the Overall Population (n = 275)

Variable			
OCT-A: interpretable exam, *n* (%)	237 (86.2)		
Signal strength <7/10	34 (12.3)		
Macular edema	2 (0.7)		
Retinal vascular disease	2 (0.7)		
Right eye, *n* (%)	136 (57)		
Angioplex: Retinal Microvasculature Features, *n* = 237	**Median**	**Q1**	**Q3**
FAZ area, mm^2	0.3	0.2	0.4
Perfusion density, unitless, ×100			
Temporal quadrant	36.6	33.7	38.5
Nasal quadrant	36.3	32.8	38.8
Superior quadrant	35.7	31.7	38.5
Inferior quadrant	35.8	32.7	38.2
Central	15.9	11.4	20.1
Inner	35.9	33.0	38.2
Full	33.7	31.0	35.7
Vessel density, mm^{-1}			
Temporal quadrant	19.8	17.9	21.0
Nasal quadrant	19.9	17.9	21.3
Superior quadrant	19.6	17.6	21.0
Inferior quadrant	19.7	17.6	21.3
Central	8.9	2.4	11.6
Inner	19.7	17.8	20.9
Full	18.6	16.4	19.7

Retinal vascular disease: age-related macular degeneration and venous occlusion.

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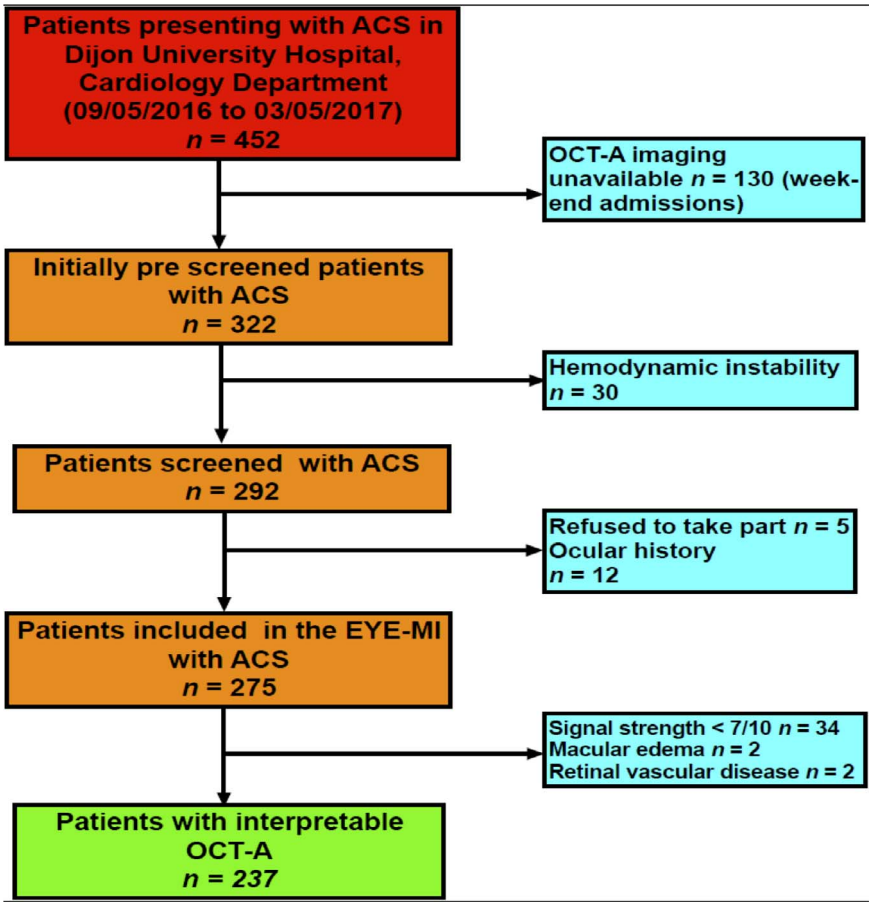

Figure 2. Flowchart of the EYE-MI study.

absence of any reference or standard regarding perifoveal vascular density, this parameter was analyzed in tertiles, the first tertile corresponding to the patients with the lowest retinal vascular densities. The reproducibility of vascular density with OCT-A was evaluated in 30 healthy volunteers. OCT-A examinations were performed three times the same day by two investigators (LA, PHG) to determine intra and interobserver reproducibility. ICCs showed a substantial reproducibility (intraobserver ICC = 0.86, 95% CI, 0.71 to 0.94; interobserver ICC = 0.89, 95% CI, 0.81–0.94).

Regarding the evaluation of controls, 44 healthy volunteers were matched 1:1 for age and sex with 44 patients of the EYE-MI study. There was a marked difference in retinal vascular density (inner vessel density) between volunteers and matched ACS patients. Inner vessel density in healthy volunteers was 21.85 mm^{-1} (20.80–22.58) and 20.30 mm^{-1} (18.60–21.20) in ACS patients ($P < 0.001$; see Supplementary Fig.).

In bivariate analysis, patients with low vascular density (first tertile of inner vessel density) were more likely than patients with a high vascular density (third tertile) to present a high burden of cardiovascular risk factors and history. They were significantly older, more frequently had a history of high blood pressure, diabetes and peripheral artery disease and had a lower LVEF at admission. No association was found between low vascular density and higher prescription rates (previous or acute) of vasoactive drugs such as beta-blockers, calcium-channel blockers or ticagrelor. Biological parameters were significantly worse in patients with low vascular density than in patients with a high vascular density (creatinine, blood glucose, HbA1c, troponin, and log NT pro-BNP levels were higher). Moreover, patients with low vascular density presented a more severe cardiovascular status as AHA risk, GRACE, SYNTAX and REACH scores were significantly higher than was the case in patients in the two other tertiles (Table 3).

Thus, to elucidate the independent determinants of retinal vascular density, we conducted a multivariate analysis of the

Table 2. Spearman's Rank Correlation Between OCT-A Microvasculature Quantitative Analysis and AHA Risk ($n = 237$)

	Spearman Correlation Coefficient
FAZ	0.170*
Perfusion density	
Temporal quadrant	−0.472†
Nasal quadrant	−0.382†
Superior quadrant	−0.463†
Inferior quadrant	−0.408†
Central	−0.349†
Inner	−0.529†
Full	−0.530†
Vessel density	
Temporal quadrant	−0.532†
Nasal quadrant	−0.454†
Superior quadrant	−0.489†
Inferior quadrant	−0.458†
Central	−0.380†
Inner	−0.540†
Full	−0.540†

* Correlation is significant with $P < 0.05$.
† Correlation is significant with a $P < 0.01$.

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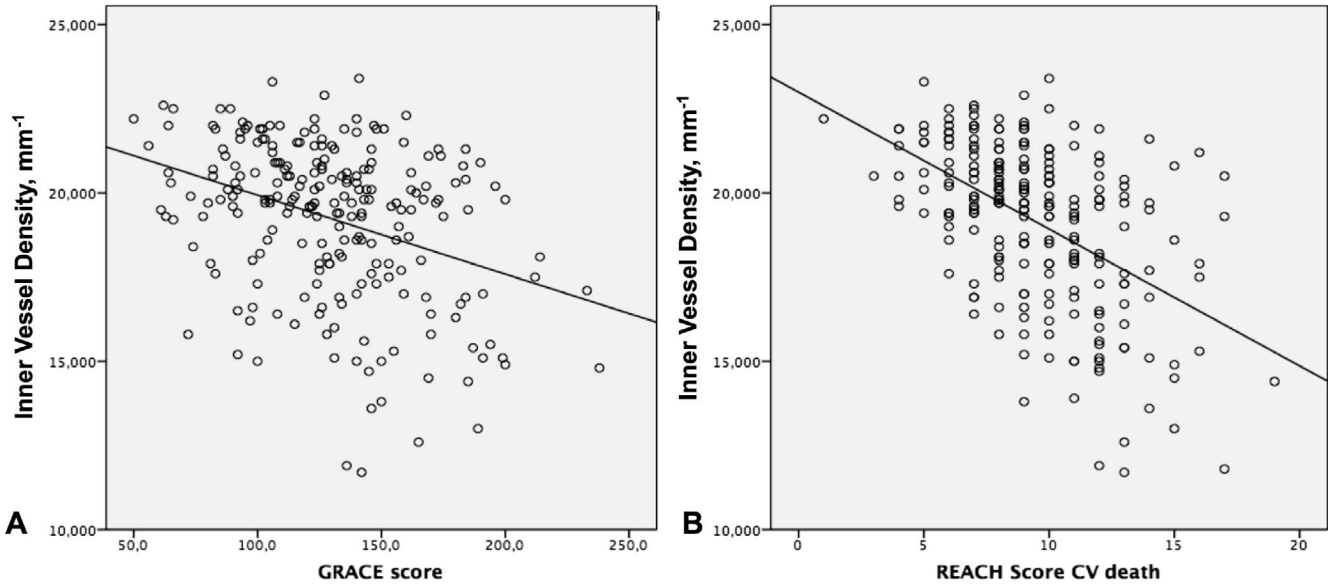

FIGURE 3. Spearman correlations between inner vessel density and both (**A**) GRACE ($r = -0.33$, $P < 0.001$) and (**B**) REACH ($r = -0.49$, $P < 0.001$) scores.

factors associated with low vascular density in bivariate analysis Two parameters were independently associated with low vascular density (first tertile). The left ventricular ejection fraction at admission was inversely associated with inner vessel density (OR, 0.95; 95% CI, 0.93–0.98; $P = 0.001$). Conversely, low vascular density was positively associated with the burden of cardiovascular risk factors, as assessed by higher AHA risk scores (OR, 1.06; 95% CI, 1.04–1.09; $P < 0.001$; Table 4). Finally, we sought to study the potential prognostic role of OCT-A in the setting of secondary prevention in our population. We found moderate correlations between inner vessel density and both the GRACE and REACH score (Spearman $r = -0.33$, $P < 0.001$ and $r = -0.49$, $P < 0.001$), respectively (Fig. 3).

DISCUSSION

To the best of our knowledge, this is the first study to explore the potential interest of assessing the retinal microvascular network using OCT-A as a means to evaluate the cardiovascular risk profile of ACS patients. Our main results are as follows:

- Vessel density is homogeneous within each retinal sector and inner vessel density on OCT-A was the quantitative retinal microvasculature finding that correlated most strongly with AHA risk.
- Inner vessel density is markedly different between volunteers and matched ACS patients.
- Inner vessel density was associated with a high burden of cardiovascular risk factors and history. Low LVEF and a high AHA risk scores were associated with low retinal vessel density assessed by OCT-A.
- Inner vessel density could reflect the cardiovascular risk profile. As OCT-A is a noninvasive imaging technique, it could become an interesting prognostic examination after ACS as it correlates with both the REACH and GRACE score.

The main finding of the present study was that retinal inner vessel density in the SCP correlated strongly with the AHA risk score (Fig. 4). This result should be interpreted as a proof-of-concept, based on the hypothesis that quantitative OCT-A vascular data could reflect the cardiovascular risk profile. Recent studies suggested the same results by showing that OCT-A can reveal microvascular changes in diabetic eyes before they can be detected by clinical examination.[28,29]

Moreover, our study showed that patients with low retinal vascular density presented indirect evidence of systemic vascular disease. Indeed, they more often had previous peripheral artery disease, impaired renal function and a history of high blood pressure and diabetes than did patients with intermediate or high vascular densities. These observations indicate that retinal microvascularization was very probably related to the cardiovascular risk profile in our population presenting with ACS.[30,31] Traditional and non-traditional risk factors play a major role in the development of epicardial lesions and nonendothelium-dependent microvascular lesions, which diminish coronary reserve. However, it is difficult to analyze myocardial microcirculation and in particular at the acute phase of the infarction as four mechanisms coexist: preexisting coronary microvascular dysfunction, specific anomalies related to the ischemia, anomalies related to reperfusion and distal emboli.[32] It can be speculated that the retinal vascular network could mirror such vascular pathological modifications. The lower LVEF and higher level of troponin after the ACS observed in the low vascular density group could be partially linked to impaired myocardial reperfusion. Low retinal vascular density in the setting of systemic microvascular dysfunction should thus be a good indicator of the impaired coronary vascularization. One of the main advantages of retinal examination with OCT-A is that it is non-invasive with a fast acquisition process. It still has to be determined whether retinal abnormalities can be detected before the systemic vascular event or if they are synchronous. Moreover, we are undertaking a study to determine whether retinal vessel density impairment is fixed or not.

We showed that the left ventricular ejection fraction on admission was significantly and independently associated with retinal vascular density in the SCP. To our knowledge, no study has investigated retinal vascularization by measuring vascular density by OCT-A in patients with a low LVEF. However, the study by Nägele et al.[33] showed that patients with heart failure presented severely impaired retinal microvascular function. This impairment is possibly linked to a defective endothelial nitric oxide signaling pathway. Furthermore, Altinkaynak et al.[34] showed that

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Table 3. Baseline Characteristics in the Three Groups According to the RVD Measured by Means of OCT-A ($n = 237$)

	Global Population, $n = 237$	Low Vascular Density Group, $n = 79$	Intermediate Vascular Density Group, $n = 79$	High Vascular Density Group, $n = 79$	*P* Value
Axial length, mm	23.43 ± 0.96	23.42 ± 0.11	23.59 ± 0.15	23.47 ± 0.11	0.618
Cardiovascular characteristics					
Age, y	**62.0 ± 13.0**	**69.8 ± 11.0*†**	**60.7 ± 10.9**	**56.0 ± 12.0**	**<0.001**
Sex, female, *n* (%)	51 (21.5)	16 (20.3)	17 (21.5)	18 (22.8)	0.928
High blood pressure history	**121 (51.0)**	**50 (63.3)*†**	**37 (46.8)**	**34 (43.0)**	**0.026**
Diabetes mellitus history	**54 (22.8)**	**27 (34.2)*†**	**16 (16.5)**	**11 (13.9)**	**0.003**
Current smoker	67 (28.3)	30 (38.0)	16 (20.3)	21 (26.6)	0.057
BMI, m^2/kg	26.7 ± 5.7	27.0 (24.0–29.7)	26.9 (23.7–30.4)	26.5 (24.5–30.6)	0.934
Hypercholesterolemia	96 (40.5)	32 (40.5)	30 (38.0)	34 (43.0)	0.810
CHD family history	80 (33.8)	27 (34.2)	23 (29.1)	30 (38.0)	0.497
Heart rate at admission, beats/min	76.1 (65.8–89.6)	75.0 (67.0–90.0)	72.0 (65–86)	71.0 (63.0–82.0)	0.060
Systolic pressure at admission, mm Hg	143.0 (120.5–167.0)	150.0 (127.8–167.5)	140.0 (117.5–170.0)	138.0 (117.0–162.0)	0.085
Diastolic pressure at admission, mm Hg	83.0 (71.0–95.0)	83.0 (75.0–91.3)	83.0 (70.0–100.0)	82.5 (70.0–95.0)	0.993
LVEF at admission, %	**55.0 (45.0–60.0)**	**50.0 (40.0–60.0)***	**60.0 (46.3–60.0)**	**60.0 (50.0–60.0)**	**0.014**
Systemic treatments					
Vasoconstrictive drugs	183 (77.2)	61 (77.2)	60 (75.9)	62 (78.5)	0.931
Beta-blockers	144 (78.7)	49 (62.0)	45 (57.0)	50 (63.3)	0.619
Calcium channel blockers	39 (21.3)	12 (15.2)	15 (19.0)	12 (15.2)	0.693
Aspirin	237 (100)	79 (100)	79 (100)	79 (100)	0.392
Statin	227 (95.8)	77 (97.5)	76 (96.2)	74 (93.7)	0.570
Ticagrelor	212 (89.4)	67 (84.8)	73 (92.4)	72 (91.1)	0.326
ACE/ARBs	180 (75.9)	57 (72.2)	61 (77.2)	62 (78.5)	0.706
Vascular history					
Ischemic coronary heart disease	51 (21.5)	22 (27.8)	14 (17.7)	15 (19.0)	0.241
Carotid atheroma	10 (0.04)	6 (7.6)	2 (2.5)	2 (2.5)	0.188
Peripheral artery disease	**12 (0.05)**	**8 (10.1)*†**	**2 (2.5)**	**2 (2.5)**	**0.042**
Chronic kidney failure	7 (0.03)	5 (6.3)	1 (1.3)	1 (1.3)	0.095
Ischemic stroke	9 (0.04)	5 (6.3)	2 (2.5)	2 (2.5)	0.354
Biology parameters					
Creatinine, µmol/L	**76.0 (64.0–92.0)**	**87.0 (71.0–104.0)*†**	**72.0 (63.0–87.0)**	**74.0 (63.0–84.0)**	**0.001**
Blood glucose level, mmol/L	**6.4 (5.4–8.2)**	**6.7 (5.7–9.2)***	**6.4 (5.4–7.7)**	**5.9 (5.1–7.4)**	**0.007**
Low-density lipoprotein cholesterol, mmol/L	**3.2 ± 1.1**	**2.9 ± 1.1*†**	**3.3 ± 1.0**	**3.3 ± 1.1**	**0.014**
High-density lipoprotein cholesterol, mmol/L	1.2 ± 0.3	1.1 (1.0–1.4)	1.1 (0.9–1.4)	1.1 (0.9–1.4)	0.554
HbA1c, %	**5.7 (5.5–6.1)**	**5.9 (5.6–6.5)***	**5.6 (5.4–6.0)**	**5.7 (5.5–6.0)**	**0.014**
Troponin level, ng/mL	**11.1 (1.9–49.0)**	**18.0 (3.9–70.5)***	**14.0 (1.0–67.0)**	**6.8 (1.6–34.0)**	**0.041**
Log NT pro-BNP, pg/mL	**5.7 (4.6–7.1)**	**6.6 (5.4–7.9)*†**	**5.4 (4.4–6.7)**	**5.3 (4.4–6.6)**	**<0.001**
Acute coronary syndrome					
STEMI	94 (39.7)	30 (38.0)	38 (48.1)	26 (32.9)	0.069
NSTEMI	113 (47.6)	43 (54.4)	28 (35.4)	42 (53.2)	
Unstable angina	30 (12.7)	6 (7.6)	13 (16.5)	11 (13.9)	
Cardiovascular risk scores					
REACH score, next cardiovascular event	**10.0 (8.0–12.0)**	**12.0 (10.0–14.0)*†**	**10.0 (8.0–12.0)**	**9.0 (7.0–11.0)**	**<0.001**
REACH score, cardiovascular death	**9.0 (7.0–11.0)**	**11.0 (9.0–13.0)*†**	**9.0 (7.0–11.0)‡**	**8.0 (6.0–9.0)**	**<0.001**
AHA risk score	**15.8 (8.5–27.2)**	**25.3 (16.8–36.4)*†**	**12.7 (7.8–24.5)‡**	**10.0 (6.2–15.8)**	**<0.001**
GRACE score	**129.7 ± 35.0**	**144.4 ± 36.8*†**	**128.5 ± 32.4**	**117.1 ± 30.9**	**<0.001**
Syntax score	**10.0 (5.0–16.0)**	**12.5 (6.0–20.0)***	**9.0 (3.0–15.0)**	**9.0 (3.8–14.3)**	**0.015**

Continuous variables as displayed as mean ± STD or median (IQR) according to their distributions. Categoric data are displayed as number (percentage). Percentages are calculated based on the number of patients with available data. Bold values indicate statistically significant results with *P* value < 0.05. ACE, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CHD, cardiovascular and heart disease; HbA1c, glycated hemoglobin; NSTEMI, non–ST-elevation myocardial infarction; NT-proBNP, n-terminal probrain natriuretic peptide; STEMI, st-elevation myocardial infarction. *P* value for trends: low, intermediate, and high vascular density group.

* Post hoc *P* (least square difference): low vs. high vascular density group statistically significant $P < 0.05$.

† Post hoc *P*: low versus intermediate vascular density group statistically significant $P < 0.05$.

‡ Post hoc *P*: intermediate vs high vascular density group statistically significant $P < 0.05$.

subfoveal choroid thickness measured with spectral domain-OCT was significantly lower in patients with heart failure. According to the authors, the pathophysiologic mechanism explaining this link was the peripheral vasoconstriction in choroid vessels in response to low cardiac output. Almeida-Freitas analyzed the ophthalmic artery with Doppler ultrasound and showed lower diastolic velocities and higher resistance indexes in patients with a low LVEF.[35] Retinal blood flow is autoregulated and maintained at a constant level by local mechanisms involving the interaction of a myogenic component and a metabolic component (in part related to the activity of glial cells).[36] In our study, the decreased retinal vascular density in patients with a LVEF could be explained by

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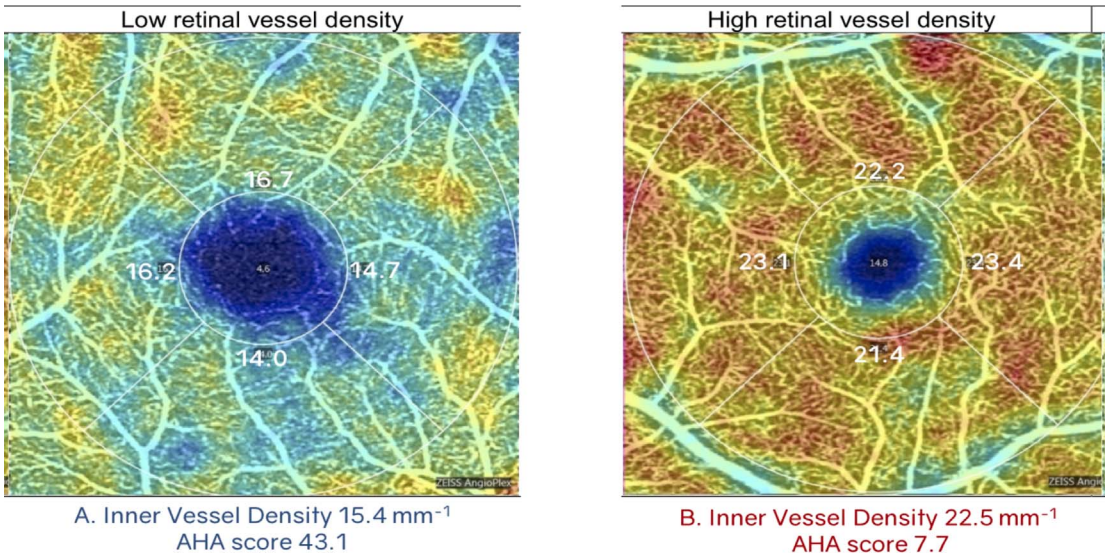

Figure 4. SCP retinal vessel density and AHA risk score (Carl Zeiss Meditec AG). Retinal vessel density analysis; a case with low retinal vessel density (inner vessel density: 15.4 mm^{-1}) and AHA = 43.1. (**A**) compared with a case of high retinal vessel density (inner vessel density 22.5 mm^{-1}) and AHA = 7.7 (**B**). The *warmer color* characterizes the highest vessel density.

impairment of the retinal blood flow local auto-regulation mechanisms. A further study should be conducted to determine the association between impaired retinal vessel density and hemodynamic parameters such as cardiac output and peripheral vascular resistance. Indeed, if such an association is confirmed, the hemodynamic status of patients should be taken into account when interpreting vascular density values.

Finally, the association between inner vessel density and the GRACE and REACH scores, that were constructed to predict the risk of major cardiovascular events after a first cardiovascular event, suggests that the analysis of retinal microvasculature with OCT-A could be considered a prognostic marker after ACS. It remains to be confirmed whether OCT-A could add any predictive value to these powerful scores, and the association between OCT-A findings and further cardiovascular events after ACS needs to be investigated. If our findings are confirmed by longitudinal studies, it could be assumed that patients with lower retinal vessel density measured with OCT-A could benefit from reinforced cardiovascular monitoring.

We acknowledge several limitations to this study. First, only participants able to have a retinal examination were included. Patients with the most severe ACS were therefore not included, which could have introduced a selection bias. Second, these findings were based on a Caucasian European population and cannot be extrapolated to other parts of the world or to other ethnic groups. Third, we did not perform carotid Doppler ultrasonography. Liao et al.[37] already showed that ipsilateral carotid artery stiffness was associated with generalized narrowing of the retinal arterioles. Our study was a cross-sectional study. It only highlighted a potential association between impaired retinal vascular density and increased cardiovascular risk. It remains to be determined whether OCT-A has any additional independent, predictive value beyond current existing risk scores (GRACE and REACH). This has to be confirmed by a longitudinal study to validate our findings. Finally, our version of the angiography software (Carl Zeiss Meditec AG) was not able to automatically measure vessel density in the deep capillary plexus on OCT-A. This limitation should be addressed with software updates in future studies. Lastly, we did not used axial length measurements to correct lateral scale of the OCT-A images which could be affected by variable ocular magnification.

In conclusion, this study strengthens the hypothesis that quantitative retinal microvasculature findings can be useful to assess the cardiovascular risk profile. Indeed, inner vascular density measured with OCT-A is associated with the cardiovascular risk profile and the left ventricular ejection fraction on admission in patients hospitalized for ACS. These preliminary results need to be confirmed in larger series, but retinal vascular density seems to be a promising biomarker of overall microvascular status and the cardiovascular risk profile.

Table 4. Univariate and Multivariate Logistic Regression Analysis to Determine Associations Between Inner Vessel Density and Baseline Characteristics

	Univariate			Multivariate		
Variable	**OR**	**95%CI**	***P***	**OR**	**95%CI**	***P***
LVEF at admission, %	0.96	0.93–0.98	0.001	0.95	0.93–0.98	0.001
AHA risk score	1.06	1.04–1.09	<0.001	1.06	1.04–1.09	<0.001
SYNTAX score	1.05	1.02–1.08	0.001			
Blood creatinine level, µmol/L	1.01	1.00–1.02	0.005			
History of peripheral artery disease	4.34	1.27–14.89	0.020			

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