REVIEW

THE AMERICAN JOURNAL of MEDICINE®

Retinal Microvascular Signs as Screening and Prognostic Factors for Cardiac Disease: A Systematic Review of Current Evidence

Raviv Allon, MD,[a] Michael Aronov, MD,[a] Michael Belkin, MD, MA,[b,c] Elad Maor, MD, PhD,[c,d] Michael Shechter, MD, MA,[c,e] Ido Didi Fabian, MD[b,c]

[a]SPRING Biomed Vision Ltd., Haifa, Israel; [b]Department of Ophthalmology, Goldschleger Eye Institute, Sheba Medical Center, Tel Hashomer, Ramat Gan, Israel; [c]Sacker Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel; [d]Heart Transplantation Unit, Leviev Cardiothoracic and Vascular Center, Sheba Medical Center, Tel Hashomer, Ramat Gan, Israel; [e]Leviev Heart Center, Sheba Medical Center, Tel Hashomer, Ramat Gan, Israel.

ABSTRACT

The substantial burden of heart disease promotes an interest in new ways of screening for early disease diagnosis, especially by means of noninvasive imaging. Increasing evidence for association between retinal microvascular signs and heart disease prompted us to systematically investigate the relevant current literature on the subject. We scrutinized the current literature by searching PubMed and Embase databases from 2000 to 2020 for clinical studies of the association between retinal microvascular signs and prevalent or incident heart disease in humans. Following exclusions, we extracted the relevant data from 42 publications (comprising 14 prospective, 26 cross-sectional, and 2 retrospective studies). Our search yielded significant associations between retinal vascular changes, including diameter, tortuosity, and branching, and various cardiac diseases, including acute coronary syndrome, coronary artery disease, heart failure, and conduction abnormalities. The findings of our research suggest that the retinal microvasculature can provide essential data about concurrent cardiac disease status and predict future risk of cardiac-related events.
 • The American Journal of Medicine (2020) 000:1–12

KEYWORDS: Acute coronary syndrome; Coronary artery disease; Fundus photography; Heart failure; Retinal vascular diameter

INTRODUCTION

Heart diseases, despite major advances in their prevention, diagnosis, and treatment over the past few decades, have remained the leading cause of death in the United States and worldwide.[1,2] Although there is wide understanding of the risk factors for heart diseases, this substantial disease burden continues to generate enduring interest in new ways to enable early diagnosis and better risk stratification.

Since the use of coronary computed tomography (CT) was first introduced into clinical practice at the beginning of this century, the focus has been concentrated on noninvasive imaging methods for assessment of the coronary microcirculation.[3] The conception of retinal vasculature as a mirror for coronary circulation is not new and is based on several observations: 1) the ophthalmic medium is translucent, allowing retinal vessels to be viewed with relative ease; 2) retinal vessels are approximately the same size as the coronary microvasculature; and 3) shown more than 80 years ago, signs of sclerosis in the retinal microvasculature of patients who are hypertensive reflect those seen in the coronary microcirculation.[4,5] At the same time, growing evidence for associations between retinal microvascular signs and heart diseases has accumulated in the peer-reviewed literature.

Funding: This study was funded by the company SPRING Biomed Vision Ltd., Haifa, Israel.

Conflicts of Interest: RA and MA are employed by SPRING Biomed Vision, and MB served as a consultant SPRING Biomed Vision. EM, MS, IDF report none.

Authorship: All authors had access to the data and a role in writing this manuscript.

Requests for reprints should be addressed to Michael Aronov, MD, 8, Haneviim St., 3rd floor, Haifa 3350109 Israel.

E-mail address: michael@springvisionbiomed.com

0002-9343/
https://doi.org/10.1016/j.amjmed.2020.07.013

The most frequently observed parameter in this research, and still at the center of attention, is retinal vascular diameter, with multiple studies examining its relationship to heart and other systemic diseases.[6–9] However, evidence derived from other geometric retinal vascular signs, including vessel tortuosity, branching angles of vessels, and fractal dimensions, has been accruing along with the development of technologies, both existing (fundus photography and fluorescein angiography) and new (such as optical coherence tomography [OCT] and OCT angiography [OCTA]). The aim of the present work is to systematically research the topic of retinal microvasculature as a screening apparatus and as a prognostic tool for heart disease.

CLINICAL SIGNIFICANCE

- Retinal microvascular signs are associated with cardiovascular diseases.
- In-depth literature review about such associations is presented in this article.
- Retinal imaging could be used as a screening, diagnostic, and prognostic tool for cardiovascular diseases.
- Retinal vascular diameter correlates with acute coronary syndrome incidence, especially in women, and can predict its occurrence.
- Retinal vascular diameter is more strongly related to acute coronary syndrome in midlife rather than in the elderly population.

METHODS

Search Strategy and Study Selection

We carried out a systematic search based on population, intervention, comparison, and outcome strategy.[10] Our study population consisted of patients with cardiovascular diseases, including ischemic heart disease, heart failure, and conduction abnormalities. For ophthalmic imaging, we included fundus color photography, fluorescein angiography, OCT and OCTA as the intervening modalities. We selected articles describing patients with heart disease and articles that compared patients with heart and non-heart disease to investigate possible associations with retinal vascular signs.

Searches were carried out in PubMed and Embase from January 1, 2000, to January 1, 2020, using the combination of search terms provided in the Supplementary Materials, available online. The articles were searched and screened by 2 independent reviewers. In the case of a disagreement, the relevant article was discussed by the reviewers until they reached consensus. The electronic search was supplemented by the authors' personal files, by hand-searching the bibliographies of papers selected from the electronic search and those of review articles.

Excluded from our research were articles discussing solely the findings of diabetic or hypertensive retinopathy. We also excluded animal studies, case reports, studies published only as abstracts or presented in conferences without full subsequent publication, studies with fewer than 10 patients, and review papers.

Retinal Microvascular Signs

We aimed to observe a wide range of retinal vascular signs, derived from fundus color photography, fluorescein angiography, OCT, and OCTA; Figures 1 and 2 illustrate some of the retinal vascular signs described herein. In the following, defined briefly, are fundus-color-photography-derived signs (fluorescein-angiography-, OCT-, and OCTA-derived signs are defined in the Supplementary Materials, available online):

(I) central retinal artery equivalent (CRAE) and central retinal vein equivalent (CRVE), measured as the average of the diameter of largest 6 arterioles and 6 venules, respectively;
(II) arteriolar-to-venular ratio (AVR), the ratio of CRAE to CRVE;
(III) simple tortuosity, the ratio of actual path length to straight-line length of a retinal vessel segment; curvature tortuosity, derived from the integral of the curvature squared along the path of the vessel, and normalized by the total path length;
(IV) focal narrowing over a constricted area of two thirds or less the widths of proximal and distal vessel segments;
(V) fractal dimension (Df) used to quantify the branching architecture of the retinal vasculature using the box-counting method;
(VI) optimality ratio, a measure of power loss in the blood flow in bifurcations related to endothelial dysfunction; optimality deviation measures the extent to which the optimality ratio deviates from the theoretically predicted optimum; and
(VII) branching angle, the first angle subtended between 2 daughter vessels at each vascular bifurcation.

RESULTS

Our literature search yielded the following numbers and types of records. After excluding duplicates, we identified 750 records with titles and abstracts that warranted initial review. We excluded 695 of them as ineligible, leaving 55 full-text articles to be further assessed for eligibility. Of those, 27 failed to meet our inclusion criteria and were excluded. The flow diagram (Figure 3), constructed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), illustrates the study selection.

Following the addition of studies identified by cross referencing, 42 studies (comprising 14 prospective cohorts, 26 cross-sectional studies, and 2 retrospective studies) met our eligibility criteria and were included in our research.

Presented next are our findings on associations between retinal microvasculature and acute coronary syndrome and coronary artery disease. Additional findings on associations

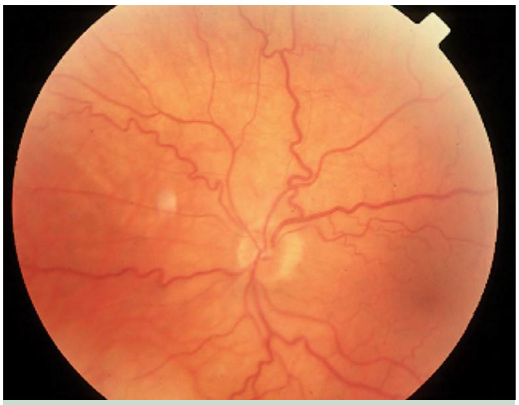

Figure 1 Increased retinal vascular tortuosity. Reprinted with permission from Rousso L, Sowka J. Recognizing Abnormal Vasculature. Review of Optometry, Jan 15, 2017; https://www.reviewoptometry.com/article/recognizing-abnormal-vasculature

with heart failure (Supplementary Table S2, available online) and conduction abnormalities are described in the Supplementary Materials, available online.

Retinal microvascular signs and acute coronary syndrome

The 11 prospective studies seeking microvascular predictors of acute coronary syndrome were drawn from 8 different cohorts with follow-up periods ranging from 3.5 to 18 years (Table 1). Of those 11 studies, retinal vascular diameter (including CRAE, CRVE, or AVR) had been measured and discussed in 10.

The Atherosclerosis Risk in Communities (ARIC), a prospective, multicenter cohort study encompassing 10,000 patients, published 3 articles in 2002, 2008, and 2016 in which these cohort populations were followed for 3.5, 8.8, and 16 years, respectively. These studies showed, in women but not in men, that lower CRAE, higher CRVE, and lower AVR were associated with incident acute coronary syndrome[11–13] and that focal arteriolar narrowing and arteriovenous nicking were not associated with incident acute coronary syndrome in either gender.[12] The gender discrepancy seen in these cohorts was also observed in a few other studies.[14–16] Regardless of the gender discrepancy described in these studies, 2 other prospective studies and 1 cross-sectional study showed that wider venular and narrower arteriolar diameter in both genders were associated with higher incidence of acute coronary syndrome.[17–19]

Some of the included prospective studies were characterized by homogeneous populations of specific patients. Miller et al showed that in a type 1 diabetes mellitus population, narrower arteriolar diameter was associated with acute coronary syndrome in women but not in men, yet venular diameter in this cohort was not associated with acute coronary syndrome in either sex.[15] In a prospective study of a large population of patients with type 2 diabetic in the Wisconsin Epidemiologic Study of Diabetic Retinopathy, no association was found between CRAE or CRVE and mortality related to acute coronary syndrome over 22 years of follow-up.[20] In a prospective study of a population of patients with chronic renal insufficiency, Grunwald et al found an association between acute coronary syndrome and wider retinal veins but not arteries.[21] The Lipid Research Clinics Coronary Primary Prevention Trial population, which included only men who were hypertensive, found that generalized or focal arteriolar narrowing tripled the risk of acute coronary syndrome and death related to acute coronary syndrome following multivariate adjustment. Arteriovenous nicking also tripled the risk, but only for

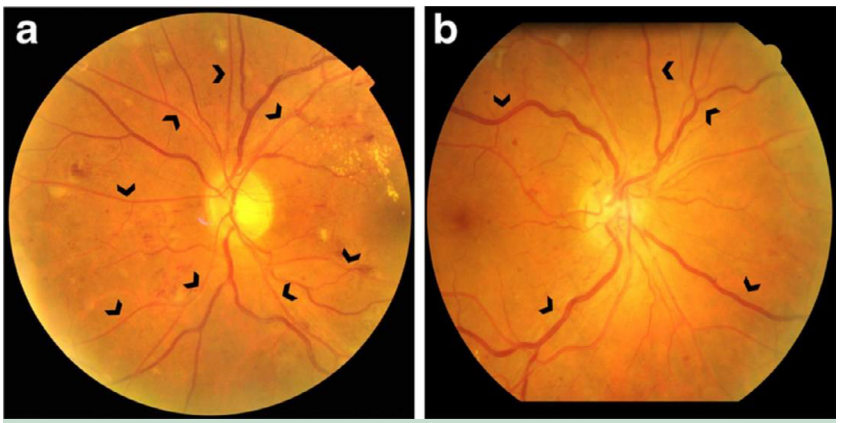

Figure 2 Examples of **(A)** narrowed retinal arterioles and **(B)** widened retinal venules (indicated by black arrows).
Reprinted with permission from Cheung CY, Ikram MK. The clinical implications of recent studies on the structure and function of the retinal microvasculature in diabetes. *Diabetologia*. 2015;58(5):871-885. doi:10.1007/s00125-015-3511-1

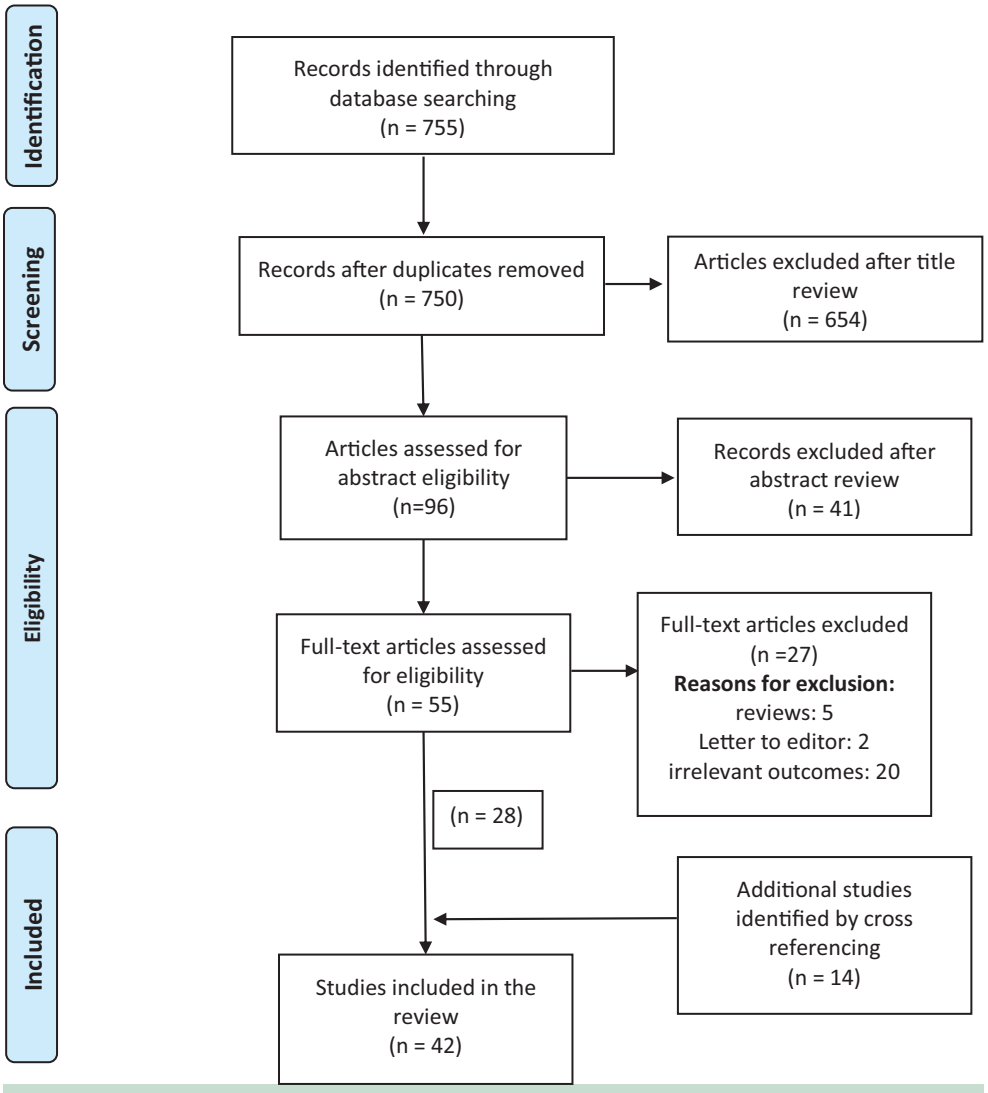

Figure 3 PRISMA flow chart for study selection.
From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. *PLoS Med*. 2009;6(7): e1000097. doi:10.1371/journal.pmed1000097 **For more information, visit** www.prisma-statement.org.

stage 1 hypertension.[22] Similar results were obtained in 1 cross-sectional study of patients with glaucoma.[23]

The predictive ability of Df to forecast death related to acute coronary syndrome was examined only in 1 prospective study.[23] Overall, patients with results in the lowest and highest quartiles of Df were found to have more risk factors for cardiovascular diseases. However, these quartiles remained significantly associated with adverse outcome following multivariate adjustment for risk factors and for retinal vascular diameter. When stratified by age, the hazard ratios were even higher in the <70-year-old age group.[24]

Age played a meaningful role in other studies as well. In a population of patients ages 65 or older without diabetes, no association was found between focal arteriolar narrowing, CRAE, or arteriovenous nicking and prevalent myocardial infarction.[25] In a case-control study within the Beaver Dam Eye Study cohort, Wong et al observed that focal narrowing, CRAE, and arteriovenous nicking were associated with any death related to cardiovascular disease in the 43- to 74-year age group but not in the 75-year and older age group. However, although the outcome "any cardiovascular disease death" in that study encompassed acute coronary syndrome, it was also much wider than that but was not stratified in the article.[26]

Some studies focused on other retinal vascular signs. In 1 such study, arteriovenous nicking and AVR did not differ between patients with acute coronary syndrome and patients with stable coronary artery disease, yet retinopathy signs differed significantly between those 2 groups.[27] Witt et al examined optimality ratios and found a positive association between optimality deviation and death from ischemic heart disease. Interestingly, these authors also found that

Table 1 Retinal Vascular Signs Obtained by Fundus Photography and Its Associations with ACS

S/N	Author	Cohort	Sample size	Demographics		Follow-up period (mean years)	Vascular parameters observed	Main results
				Age (mean years)	Male gender (%)			
Prospective studies								
1	Wong (2002)[19]	ARIC Study	N = 9648	60	—	3.5	AVR	In women, lower AVR increased ACS incidence (RR 1.5; CI 95% 1.1-2)
2	McGeechan (2008)[20]	ARIC Study	N = 9155	60	41.7	8.8	CRAE, CRVE, Focal narrowing, AV nicking, Retinopathy	In women, narrower CRAE increased ACS incidence (by 1.31 per SD decrease [CI 95% 1.10-1.56]
3	Seidelmann (2016)[21]	ARIC Study	N = 10,470	60	—	16	CRAE, CRVE, AVR	In women, narrower CRAE (by 1.13 per 1 SD [CI 95% 1.03-1.24]) and wider CRVE (by 1.1 per 1 SD [CI 95% 1-1.2]) increased ACS incidence.
4	Wang (2006)[22]	The Blue Mountains Eye Study	N = 3340	64-67[†]	43.5	9	CRAE, CRVE, AVR	In women, narrower CRAE increased ACS-related death incidence (by 1.9 per 1 SD decrease [CI 95% 1-3.5]
5	Miller (2009)[23]	Pittsburgh Epidemiology of Diabetes Complications Study	N = 448	30.6 for ACS cases 24.3 for non-cases	50	18	CRAE, CRVE, AVR, Retinopathy	In women, narrower CRAE increased ACS incidence (RR 1.92; 95% CI 1. 24-2.96)
6	Wong (2006)[25]	The Cardiovascular Health Study	N = 1992	79	38-43	5	CRAE, CRVE, AVR, focal narrowing, AV nicking, retinopathy	Narrower CRAE (RR 3, 95% CI 1.6-5.7) and wider CRVE (RR 2; 95% CI 1. 1-3.7) increased ACS incidence
7	Wang (2007)[26]	The Beaver Dam Eye Study, The Blue Mountains Eye Study	N = 7494	63	44.1	10.9	CRAE, CRVE	Narrower CRAE (RR 1.34, 95% CI 1.1-1.6) and wider CRVE (RR 1.24; 95% CI 1.02-1.52) increased ACS-related death

Table 1 (*Continued*)

S/N	Author	Cohort	Sample size	Demographics		Follow-up period (mean years)	Vascular parameters observed	Main results
				Age (mean years)	Male gender (%)			
8	Klein (2007)[28]	Wisconsin Epidemiologic Study of Diabetic Retinopathy	N = 962	64.5	45.2	4-10	CRAE, CRVE	Narrower CRAE increased ACS-related death incidence in univariate but not in multivariate analysis (RR 1.21; 95% CI 0.98-1.51)
9	Grunwald (2012)[29]	The Chronic Renal Insufficiency Cohort	N = 1820	60	54.7	—	CRVE, CRAE, Retinopathy	Wider CRVE showed a trend toward incident MI (RR 1.40; 95% CI 0.95-2.06)
10	Duncan (2002)[30]	The Lipid Research Clinic's Coronary Primary Prevention Trial	N = 560	51.3 for cases 48.9 for non-cases	100	7.8	Retinopathy, CRAE, focal narrowing	Narrower CRAE or focal narrowing increased ACS incidence (RR 2.9; 95% CI 1.3-6.2).
11	Liew (2010)[32]	The Blue Mountains Eye Study	N = 3303	64-71†	39.7-46	14	Df	Suboptimal Df (highest and lowest quartiles) were associated with ACS related death (RR 1.89; 95% CI 1.2-2.8).
Cross-sectional studies								
12	Liew (2019)[24]	The Australian Heart Eye Study	N = 915	59.9-65†	75.8	—	CRAE, CRVE	In women, Narrower CRVE was associated with microvascular angina (OR 3.5; 95%CI 1.3-9.24)
13	Øhrn (2018)[27]	The Tromsø Study	N = 6128	62.7-69.7†	30-61	—	CRAE, CRVE	Unrecognized MI was associated with narrower CRAE compared to recognized MI (OR 1.66; 95% CI 1.0—2.62(
14	Lam (2006)[31]	—	N = 116	71	37.9	—	Focal narrowing	Focal narrowing was not associated with ACS
15	Wong (2003)[33]	The Cardiovascular Health Study	N = 2050	77*	38.9	—	Retinopathy, CRAE, focal narrowing, arteriovenous nicking	Retinopathy was associated with ACS. (OR 1.7; 95%CI 1.1-2.8)
16	Kralev (2010)[35]	—	N = 62	63.4 for cases 65.4 for non-cases	67 in cases 74 in non-cases	—	Retinopathy, focal narrowing, AV nicking, AVR	Retinopathy was more frequent in ACS compared to CAD patients. (OR 11.7; 95% CI 1.4-96.5)

Table 1 (*Continued*)

S/N	Author	Cohort	Sample size	Demographics		Follow-up period (mean years)	Vascular parameters observed	Main results
				Age (mean years)	Male gender (%)			
Retrospective studies								
17	Wong (2002)[34]	The Beaver Dam Eye Study	N = 1611	–	50-53	–	Retinopathy, Focal narrowing, arteriovenous (AV) nicking, CRAE, AVR	Retinopathy, focal narrowing, arteriovenous nicking and CRAE were associated with CVD death (including ACS) in 43- to 75-age group.
18	Witt (2006)[36]	The Beaver Dam Eye Study	N = 700	64	63	–	AVR, Optimality deviation, Simple tortuosity, Curvature tortuosity	Lower AVR, lower tortuosity and higher optimality deviation were associated with ACS related death.

ACS = acute coronary syndrome; ARIC= Atherosclerosis Risk in Communities; AV = arteriovenous; AVR = arteriolar-to-venular ratio; CAD = coronary artery disease; CI = Confidence interval; CRAE = central retinal artery equivalent; CRVE = central retinal venous equivalent; CVD = cardiovascular disease; Df = fractal dimension; MI =myocardial infraction; OR: odds ratio; RR = relative risk; SD = standard deviation.
*Median.
†Ranges of means between different study groups.

lower arteriolar tortuosity (ie, straighter arterioles) was associated with such death. Both effects persisted after adjustment for age, gender, and other cardiovascular risk factors.[28]

Among the 27 cross-sectional studies that were included in our research were 3 that reported vascular findings obtained by OCTA and by spectral domain OCT. Results from these studies are summarized in Supplementary Results, available online.

Retinal microvascular signs and coronary artery disease

Retinal vascular diameter was examined in all 9 of the studies in which retinal photographs had been used to detect inconsistent results (Table 2). In most cases, CRAE, CRVE and AVR were not associated with the extent of coronary artery disease examined by different evaluation methods (ie, Leamen score,[29,30] syntax score,[16] coronary artery calcification,[31] or coronary computed tomography angiography (CCTA).[32] A few of these studies, however, did find associations between these entities: Gopinath et al found that in women, narrower CRAE or wider CRVE was significantly associated with higher Gensini and Extent scores for coronary artery disease, but these associations were not observed in men.[33] Wang et al showed that narrower CRAE was associated with lower hyperemic myocardial blood flow when examined by cardiac magnetic resonance imaging (MRI) but found that this association depended on the extent of coronary calcification, existing in patients with no coronary plaque calcification but not in those with even minimal calcium scores.[34] In a recent study in which the intracoronary plaque composition was examined,[35] larger CRAE was found to be associated with a calcific plaque and smaller CRAE with a lipid plaque. Noncalcified atherosclerotic plaques are often more metabolically active than heavily calcified plaques and are associated with increased risk of acute coronary syndromes,[36] so that the finding that calcific and lipid plaque groups differed significantly in their cardiovascular disease risk-factor rates was a major limitation of the study. In a recent OCTA study, lower retinal arterial lumen diameter, retinal arterial outer diameter, and AVR were all found to be associated with the extent of coronary artery disease in patients presenting with acute coronary syndrome. The analysis, however, was not adjusted for cardiovascular disease risk factors.[37]

Wang et al observed that retinal vessel geometric measures such as Df, curvature tortuosity, and branching angle lower arteriolar and venular curvature tortuosity (meaning straighter retinal venules and arteries) were associated with coronary artery disease Extent and Gensini scores. In a subgroup of patients who had undergone cataract surgery, it was found that lower Df, arteriolar branching angle, and CRAE were associated with coronary artery disease vessel scores. In that study, a combined retinal score was

Table 2 Associations Between Retinal Vascular Signs and CAD

S/N	Author	Cohort	Sample size	Demographics		Coronary artery parameter observed	Vascular parameters observed	Main result
				Age (mean years)	Male gender (%)			
Retinal vascular signs obtained by fundus photography								
1	Liew (2019)[24]	The Australian Heart Eye Study	N = 776	—	78	SYNTAX score	CRAE, CRVE	CRAE and CRVE were not associated with syntax score
2	Kreis (2009)[40]	—	N = 98	64	—	Leamen score, diseased vessel score, LAD stenosis>70%	CRAE, CRVE	CRAE and CRVE were not associated with Leamen score
3	Cheng (2018)[41]	—	N = 144	61	70	Leamen score, diseased vessel score, LAD stenosis>70%, TIMI myocardial perfusion score	CRAE, CRVE, focal narrowing, arteriovenous nicking	CRAE and CRVE were not associated with Leamen score. Retinopathy was associated with higher Leamen score and TIMI blush score
4	Wong (2007)[42]	Multi-Ethnic Study of Atherosclerosis	N = 5971	59.6-70.2*	36.8-66.5	CAC	Retinopathy, CRAE, CRVE, arteriovenous nicking, focal narrowing	CRAE and CRVE were not associated with CAC scores. Retinopathy (OR 1.4; 95% CI 1.1-1.7) and AV nicking were associated with moderate to severe CAC scores
5	Josef (2013)[43]	—	N = 51	53 for cases 51 for non-cases	85	CCTA	AVR	AVR was not associated with CAD (OR 1.5; 95% CI 0.5-1.5)
6	Gopinath (2014)[44]		N = 1120	—	74	Diseased vessel score, Gensini score, Extent score	CRAE, CRVE	In women, narrower CRAE and wider CRVE were associated with higher Gensini and Extent scores. (OR 2.99; 95% CI 1.45-6.16)
7	Wang (2008)[45]	Multi-Ethnic Study of Atherosclerosis	N = 212	—	56.6	Myocardial blood flow using cardiac MRI	CRAE, CRVE	Arrower CRAE was associated with lower myocardial blood flow
8	Wightman (2019)[46]	—	N = 28	62	79	Coronary plaque OCT, Diseased vessel score	Retinopathy, CRAE, CRVE	larger CRAE was associated with a calcific plaque, narrower CRAE with a lipid plaque.

Table 2 (*Continued*)

S/N	Author	Cohort	Sample size	Demographics		Coronary artery parameter observed	Vascular parameters observed	Main result
				Age (mean years)	Male gender (%)			
9	Wang (2018)[48]	The Australian Heart Eye Study	N = 1187	61	76	Diseased vessel score, Gensini score, Extent score	Df, curvature tortuosity, branching angle, CRAE, CRVE	Lower curvature tortuosity was associated with Gensini and Extent scores. Lower Df, lower branching angles and lower CRAE were associated with higher vessel scores
Retinal vascular signs obtained by fluorescence angiography								
10	Koç (2013)[49]	—	N = 60	52.2 for cases 49.9 for non-cases	72.4-77.4	TIMI frame score	ART, AVP	TIMI score positively correlated with ART and AVP time
11	Taha (2018)[50]	—	N = 105	49.5-53.5*	—	TIMI frame score	ART, AVP	Higher ART and AVP time were associated with higher TIMI scores
Retinal vascular signs obtained by optical coherence tomography angiography								
12	Xu (2019)[39]	—	N = 186	64.5 for cases 62.7 for non-cases	56.1-70.3	Angiography primary and secondary branch stenosis	Retinal arterial and venular outer and lumen diameter, arterial and venous wall thickness, AVR	Lower AVR and retinal arterial lumen and outer diameter were associated with the extent of CAD in patients presenting with ACS
13	Yang (2019)[51]		N = 146	54.2	38.9	CAD on registry	Capillary flow density	CAD was associated with lower capillary flow density (OR -3.206; 95% CI -5.766, -0.645)
14	Wang (2019)[52]	—	N = 316	66.3 for cases 64.4 for non-cases	79.5-83.7	Gensini score	Capillary flow density	Lower vascular density and blood flow were found in superficial, deep and choroid capillary layers in CAD patients. Gensini score was associated with lower choroidal and retinal capillary flow density

ART = arm-retina time; AV = arteriovenous; AVP = arteriovenous passage; AVR = arteriolar-to-venular ratio; CAC = coronary artery calcification; CAD = coronary artery disease; CCTA = coronary computed tomography angiography; CI = confidence interval; CRAE = central retinal artery equivalent; CRVE = central retinal venous equivalent; Df = fractal dimension; LAD = left anterior descending; OR = odds ratio.

*Ranges of means between different study groups.

constructed from the variables that were the most strongly correlated in the multivariate analysis, namely Df, arteriolar curvature tortuosity, and retinal arteriolar diameter. In patients with this combined score, the odds of having a stenosis greater than 50% in any coronary artery segment were increased by 3-fold, as were the odds of having obstructive coronary stenosis in all 3 main coronary arteries.[38]

Other means of retinal imaging, such as fluorescein angiography and OCTA, have also been explored, as presented in the Supplementary Materials, available online.

DISCUSSION

A major finding of our systematic review was that vascular diameter, and specifically narrower CRAE, wider CRVE, and smaller AVR, correlate with the incidence of acute coronary syndrome, especially in women, and can predict its occurrence. The gender discrepancy seen in our research has been discussed in previous reviews[7,8,39] and supports the hypothesis that microvascular dysfunction plays a greater role in the pathogenesis of coronary heart disease in women than in men.[40] This notion is clinically borne out in studies showing that compared to men, women have higher rates of acute coronary syndrome with atypical symptoms and higher rates of microvascular angina with angiographic findings of no significant coronary artery disease.[16] Also, in women and men with the same finding, the prognosis in women is worse.[40,41] As with gender, age stratification was also seen here to be meaningful. We found a few studies showing that retinal vascular signs, and particularly diameter, tend to be more strongly related or to have any relationship at all with acute coronary syndrome in the midlife rather than in the elderly population. These findings are supported by findings in a cohort published prior to the time frame of the present research,[42] as well as in later studies examining relationships between age and other cardiovascular disease and risk factors, including blood pressure,[43] impaired fasting glucose,[44] incident diabetes,[45] and stroke.[46] Although there is no satisfactory explanation for this phenomenon as yet, it points to the advisability of including retinal vascular signs when screening for cardiovascular diseases in midlife age groups and supports the use of age-group stratification in further studies.

An interesting finding of our research was that measurements of retinal vascular diameter are not as strongly correlated with the presence and extent of coronary artery disease measures obtained by different imaging methods and classifications. On one hand, the fact that vascular diameter is associated with acute coronary syndrome but not with coronary artery disease is surprising, given that the extent of coronary artery disease was consistently reported in the literature over the years to be an independent predictor of acute coronary syndrome.[47–49] On the other hand, this apparent discrepancy coincides with the hypothesis that retinal vascular diameter as a predictor of "acute coronary syndrome events" lies in microvascular dysfunction rather than macrovascular disease.

Our research revealed associations between different geometric retinal vascular signs and various cardiac diseases:

1. Lower arterial tortuosity (straighter arteries) was found to be associated with death related to acute coronary syndrome and extent of coronary artery disease. Those associations were evident following adjustments for cardiovascular disease risk factors such as older age, hypertension, and higher body mass index, which were also found in prior studies to be associated with lower tortuosity.[50] A few possible explanations of these connections have been offered: Witt et al suggested that reduced tortuosity may be linked to endothelial dysfunction and impaired oxygenation,[28] while Vorobtsova et al suggested that reduced tortuosity increases coronary wall shear stress, thereby providing protection against atherosclerosis.[51]
2. Deviation from the bifurcation optimality ratio was found to be positively associated with death related to acute coronary syndrome. Lower branching angle was found to be associated with the prevalence of coronary artery disease. Associations of branching angle with aging,[52] with peripheral vascular disease,[53] and with severity of diabetic retinopathy[54] have been reported in the literature, and could be indicators of endothelial function.[55]
3. Df was reported to have a U-shaped association with both the occurrence of death related to acute coronary syndrome and the prevalence of atrial fibrillation, and a reduced Df was also shown to be associated with the prevalence of coronary artery disease. This U-shaped relationship was depicted by Sng et al to also coexist with the prevalence of chronic kidney disease.[56] It could also explain the inconsistent results in which both low Df and high Df were found to be associated with stroke[57–61] and with diabetic retinopathy.[62–64] Liew et al offered an explanation of the U-shaped relationship by suggesting that on the one hand rarefaction of the microcirculation could prevent the formation of collaterals and, thus, predispose the patient to ischemia, while on the other hand a vast microcirculatory architecture could also be a marker of ischemia.[24]

Most of the original articles and reviews published on the subject of relations between retinal vascular signs and heart disease over the past 2 decades have focused on vascular diameter.[6,9,65] However, as with vascular diameter, most of the vascular signs mentioned previously were extracted from simple fundus photography and suggest that microvascular health is maintained both by adequate vascular diameters and by optimal branching architecture. At this stage the added value of these signs over vascular diameter is unclear because in most of the relevant articles the results were not adjusted for vascular diameter, which could have pinpointed its contribution, as seen in the study by Liew et al.[24] Another important step for further studies, as also

seen in that study,[23] could be to design and use models with a few retinal vascular signs, which could raise prediction levels and exclude overlapping signs.

Variance was observed in the statistical analyses employed in the different studies. Some studies did not use multivariate or multilinear analysis (Supplementary Table S1, available online). Arguably, lack of adjustments for cardiovascular disease risk factors may jeopardize the conclusions of a study because cardiac diseases are multifactorial. A few studies with homogeneous populations suggested that cardiovascular diseases may affect the predictive pattern of the retinal microvascular signs,[20–23] emphasizing the importance of adjustment for cardiovascular disease factors. This review also shows that stratification of results for gender is critical, given the likelihood of pathophysiological differences existing between genders.

CONCLUSION AND FURTHER STUDY

In conclusion, the findings of our research demonstrate that retinal vascular signs differ in their associations with heart diseases. Retinal vascular diameter was found to correlate with acute coronary syndrome events and predict them, especially in women, but it was not strongly associated with macrovascular coronary artery disease. Further work should focus, by means of coronary angiography or other noninvasive imaging modalities, on the connection between retinal vascular findings and microvascular coronary function.

Finally, our research findings suggest that more accurate models should be designed and used for specific patient populations. Further studies in this area should adopt methodological principles of using multilinear adjustment models for cardiovascular disease risk factors and different retinal vascular signs and their stratification by gender and age.

References

1. World Health Organization. The top 10 causes of death. Available at:http://www.who.int/mediacentre/factsheets/fs310/en/. Accessed September 14, 2019.
2. Murphy SL, Xu J, Kochanek KD, Arias E. Mortality in the United States, 2017. *NCHS Data Brief* 2018:(328):1–8.
3. Neglia D, Rovai D, Caselli C, et al. Detection of significant coronary artery disease by noninvasive anatomical and functional imaging. *Circ Cardiovasc Imaging* 2015;8(3):e002179. https://doi.org/10.1161/CIRCIMAGING.114.002179.
4. Scheie HG. Evaluation of ophthalmoscopic changes of hypertension and arteriolar sclerosis. *AMA Arch Ophthalmol* 1953;49(2):117–38.
5. Moritz AR, Oldt MR. Arteriolar sclerosis in hypertensive and nonhypertensive individuals. *Am J Pathol* 1937;13(5):679.
6. Sun C, Wang JJ, Mackey DA, Wong TY. Retinal vascular caliber: systemic, environmental, and genetic associations. *Surv Ophthalmol* 2009;54(1):74–95.
7. McGeechan K, Liew G, Macaskill P, et al. Meta-analysis: retinal vessel caliber and risk for coronary heart disease. *Ann Intern Med* 2009;151(6):404–13.
8. McClintic BR, McClintic JI, Bisognano JD, Block RC. The relationship between retinal microvascular abnormalities and coronary heart disease: a review. *Am J Med* 2010;123(4):374.e1–7.
9. Dumitrescu AG, Voinea L, Badarau IA, Paun VA, Schowe M, Ciuluvica R. Update on retinal vascular caliber. *Rom J Ophthalmol* 2017;61(3):171.
10. Santos CM da C, Pimenta CA de M, Nobre MRC. The PICO strategy for the research question construction and evidence search. *Rev Lat Am Enfermagem* 2007;15(3):508–11.
11. Wong TY, Klein R, Sharrett AR, et al. Retinal arteriolar narrowing and risk of coronary heart disease in men and women: the Atherosclerosis Risk in Communities Study. *JAMA* 2002;287(9):1153–9.
12. McGeechan K, Liew G, Macaskill P, et al. Risk prediction of coronary heart disease based on retinal vascular caliber (from the Atherosclerosis Risk In Communities [ARIC] Study). *Am J Cardiol* 2008;102(1):58–63.
13. Seidelmann SB, Claggett B, Bravo PE, et al. Retinal vessel calibers in predicting long-term cardiovascular outcomes: the atherosclerosis risk in communities study. *Circulation* 2016;134(18):1328–38.
14. Wang JJ, Liew G, Wong TY, et al. Retinal vascular calibre and the risk of coronary heart disease-related death. *Heart* 2006;92(11):1583–7. https://doi.org/10.1136/hrt.2006.090522.
15. Miller RG, Prince CT, Klein R, Orchard TJ. Retinal vessel diameter and the incidence of coronary artery disease in type 1 diabetes. *Am J Ophthalmol* 2009;147(4):653–60.
16. Liew G, Mitchell P, Chiha J, et al. Retinal microvascular changes in microvascular angina: findings from the Australian Heart Eye Study. *Microcirculation* 2019:e12536.
17. Wong TY, Kamineni A, Klein R, et al. Quantitative retinal venular caliber and risk of cardiovascular disease in older persons: the cardiovascular health study. *Arch Intern Med* 2006;166(21):2388–94.
18. Wang JJ, Liew G, Klein R, et al. Retinal vessel diameter and cardiovascular mortality: pooled data analysis from two older populations. *Eur Heart J* 2007;28(16):1984–92.
19. Øhrn AM, Schirmer H, von Hanno T, et al. Small and large vessel disease in persons with unrecognized compared to recognized myocardial infarction: The TromsøStudy 2007-2008. *Int J Cardiol* 2018;253:14–9.
20. Klein R, Klein BEK, Moss SE, Wong TY. Retinal vessel caliber and microvascular and macrovascular disease in type 2 diabetes: XXI: the Wisconsin Epidemiologic Study of Diabetic Retinopathy. *Ophthalmology* 2007;114(10):1884–92. https://doi.org/10.1016/j.ophtha.2007.02.023.
21. Grunwald JE, Ying G-S, Maguire M, et al. Association between retinopathy and cardiovascular disease in patients with chronic kidney disease (from the Chronic Renal Insufficiency Cohort [CRIC] Study). *Am J Cardiol* 2012;110(2):246–53.
22. Duncan BB, Wong TY, Tyroler HA, Davis CE, Fuchs FD. Hypertensive retinopathy and incident coronary heart disease in high risk men. *Br J Ophthalmol* 2002;86(9):1002–6.
23. Lam A, Bunya VY, Piltz−Seymour JR. Cardiovascular risk factors and events in glaucoma patients with peripapillary focal arteriolar narrowing. *Acta Ophthalmol Scand* 2006;84(1):69–73.
24. Liew G, Mitchell P, Rochtchina E, et al. Fractal analysis of retinal microvasculature and coronary heart disease mortality. *Eur Heart J* 2010;32(4):422–9.
25. Wong TY, Klein R, Sharrett AR, et al. The prevalence and risk factors of retinal microvascular abnormalities in older persons: The Cardiovascular Health Study. *Ophthalmology* 2003;110(4):658–66. https://doi.org/10.1016/S0161-6420(02)01931-0.
26. Wong TY, Klein R, Nieto FJ, et al. Retinal microvascular abnormalities and 10-year cardiovascular mortality: a population-based case-control study. *Ophthalmology* 2003;110(5):933–40.
27. Kralev S, Zimmerer E, Buchholz P, et al. Microvascular retinal changes in patients presenting with acute coronary syndromes. *Microvasc Res* 2010;79(2):150–3.
28. Witt N, Wong TY, Hughes AD, et al. Abnormalities of retinal microvascular structure and risk of mortality from ischemic heart disease and stroke. *Hypertension* 2006;47(5):975–81.
29. Kreis AJ, Nguyen TT, Wang JJ, et al. Are retinal microvascular caliber changes associated with severity of coronary artery disease in symptomatic cardiac patients? *Microcirculation* 2009;16(2):177–81.

30. Cheng L, Barlis P, Gibson J, et al. Microvascular retinopathy and angiographically-demonstrated coronary artery disease: a cross-sectional, observational study. *PLoS One* 2018;13(5):e0192350.
31. Wong TY, Cheung N, Islam FMA, et al. Relation of retinopathy to coronary artery calcification: the multi-ethnic study of atherosclerosis. *Am J Epidemiol* 2007;167(1):51–8.
32. Josef P, Ali I, Ariel P, Alon M, Nimer A. Relationship between retinal vascular caliber and coronary artery disease in patients with non-alcoholic fatty liver disease (NAFLD). *Int J Environ Res Public Health* 2013;10(8):3409–23.
33. Gopinath B, Chiha J, Plant AJH, et al. Associations between retinal microvascular structure and the severity and extent of coronary artery disease. *Atherosclerosis* 2014;236(1):25–30.
34. Wang L, Wong TY, Sharrett AR, Klein R, Folsom AR, Jerosch-Herold M. Relationship between retinal arteriolar narrowing and myocardial perfusion: multi-ethnic study of atherosclerosis. *Hypertension* 2008;51(1):119–26.
35. Wightman A, Barlis P, MacBain M, et al. Small vessel disease and intracoronary plaque composition: a single centre cross-sectional observational study. *Sci Rep* 2019;9:4215.
36. Motoyama S, Ito H, Sarai M, et al. Plaque characterization by coronary computed tomography angiography and the likelihood of acute coronary events in mid-term follow-up. *J Am Coll Cardiol* 2015;66(4):337–46.
37. Xu BL, Zhou WL, Zhu TP, et al. A full-width half-maximum method to assess retinal vascular structural changes in patients with ischemic heart disease and microvascular anginga. *Sci Rep* 2019;9(1):11019. https://doi.org/10.1038/s41598-019-47194-5.
38. Wang SB, Mitchell P, Liew G, et al. A spectrum of retinal vasculature measures and coronary artery disease. *Atherosclerosis* 2018;268:215–24.
39. Wong TY, McIntosh R. Systemic associations of retinal microvascular signs: a review of recent population−based studies. *Ophthalmic Physiol Opt* 2005;25(3):195–204.
40. Merz CNB, Shaw LJ, Reis SE, et al. Insights from the NHLBI-Sponsored Women's Ischemia Syndrome Evaluation (WISE) Study: Part II: gender differences in presentation, diagnosis, and outcome with regard to gender-based pathophysiology of atherosclerosis and macrovascular and microvascular cor. *J Am Coll Cardiol* 2006;47(3 Supplement):S21–9.
41. Dean J, Cruz S Dela, Mehta PK, Merz CNB. Coronary microvascular dysfunction: sex-specific risk, diagnosis, and therapy. *Nat Rev Cardiol* 2015;12(7):406.
42. Gillum RF. Retinal arteriolar findings and coronary heart disease. *Am Heart J* 1991;122(1 Pt 1):262.
43. Wong TY, Klein R, Klein BEK, Meuer SM, Hubbard LD. Retinal vessel diameters and their associations with age and blood pressure. *Invest Ophthalmol Vis Sci* 2003;44(11):4644–50.
44. Kifley A, Wang JJ, Cugati S, Wong TY, Mitchell P. Retinal vascular caliber and the long−term risk of diabetes and impaired fasting glucose: the Blue Mountains Eye Study. *Microcirculation* 2008;15(5):373–7.
45. Klein R, Klein BEK, Moss SE, Wong TY. The relationship of retinopathy in persons without diabetes to the 15-year incidence of diabetes and hypertension: Beaver Dam Eye Study. *Trans Am Ophthalmol Soc* 2006;104:98.
46. Wong TY, Klein R, Couper DJ, et al. Retinal microvascular abnormalities and incident stroke: the Atherosclerosis Risk in Communities Study. *Lancet* 2001;358(9288):1134–40.
47. Arbab-Zadeh A, Fuster V. The myth of the "vulnerable plaque": transitioning from a focus on individual lesions to atherosclerotic disease burden for coronary artery disease risk assessment. *J Am Coll Cardiol* 2015;65(8):846–55.
48. Pletcher MJ, Tice JA, Pignone M, Browner WS. Using the coronary artery calcium score to predict coronary heart disease events: a systematic review and meta-analysis. *Arch Intern Med* 2004;164(12):1285–92.
49. Bamberg F, Sommer WH, Hoffmann V, et al. Meta-analysis and systematic review of the long-term predictive value of assessment of coronary atherosclerosis by contrast-enhanced coronary computed tomography angiography. *J Am Coll Cardiol* 2011;57(24):2426–36.
50. Cheung CY, Zheng Y, Hsu W, et al. Retinal vascular tortuosity, blood pressure, and cardiovascular risk factors. *Ophthalmology* 2011;118(5):812–8.
51. Vorobtsova N, Chiastra C, Stremler MA, Sane DC, Migliavacca F, Vlachos P. Effects of vessel tortuosity on coronary hemodynamics: an idealized and patient-specific computational study. *Ann Biomed Eng* 2016;44(7):2228–39.
52. Stanton AV, Wasan B, Cerutti A, et al. Vascular network changes in the retina with age and hypertension. *J Hypertens* 1995;13(12 Pt 2):1724–8.
53. Chapman N, Dell'Omo G, Sartini MS, et al. Peripheral vascular disease is associated with abnormal arteriolar diameter relationships at bifurcations in the human retina. *Clin Sci* 2002;103(2):111–6.
54. Habib MS, Al-Diri B, Hunter A, Steel DHW. The association between retinal vascular geometry changes and diabetic retinopathy and their role in prediction of progression—an exploratory study. *BMC Ophthalmol* 2014;14(1):89.
55. Griffith TM, Edwards DH, Davies RL, Harrison TJ, Evans KT. EDRF coordinates the behaviour of vascular resistance vessels. *Nature* 1987;329(6138):442.
56. Sng CCA, Sabanayagam C, Lamoureux EL, et al. Fractal analysis of the retinal vasculature and chronic kidney disease. *Nephrol Dial Transplant* 2010;25(7):2252–8. https://doi.org/10.1093/ndt/gfq007.
57. McGrory S, Ballerini L, Doubal FN, et al. Retinal microvasculature and cerebral small vessel disease in the Lothian Birth Cohort 1936 and Mild Stroke Study. *Sci Rep* 2019;9(1):6320.
58. Kawasaki R, Azemin MZC, Kumar DK, et al. Fractal dimension of the retinal vasculature and risk of stroke: a nested case-control study. *Neurology* 2011;76(20):1766–7.
59. Cheung CY, Tay WT, Ikram MK, et al. Retinal microvascular changes and risk of stroke: the Singapore Malay Eye Study. *Stroke* 2013;44(9):2402–8.
60. Doubal FN, MacGillivray TJ, Patton N, Dhillon B, Dennis MS, Wardlaw JM. Fractal analysis of retinal vessels suggests that a distinct vasculopathy causes lacunar stroke. *Neurology* 2010;74(14):1102–7.
61. Cheung N, Liew G, Lindley RI, et al. Retinal fractals and acute lacunar stroke. *Ann Neurol* 2010;68(1):107–11.
62. Grauslund J, Green A, Kawasaki R, Hodgson L, Sjolie AK, Wong TY. Retinal vascular fractals and microvascular and macrovascular complications in type 1 diabetes. *Ophthalmology* 2010;117(7):1400–5. https://doi.org/10.1016/j.ophtha.2009.10.047.
63. Cheung N, Donaghue KC, Liew G, et al. Quantitative assessment of early diabetic retinopathy using fractal analysis. *Diabetes Care* 2009;32(1):106–10.
64. Lim LS, Chee ML, Cheung CY, Wong TY. Retinal vessel geometry and the incidence and progression of diabetic retinopathy. *Invest Ophthalmol Vis Sci* 2017;58(6):BIO200–5.
65. Newman AR, Andrew NH, Casson RJ. Review of paediatric retinal microvascular changes as a predictor of cardiovascular disease. *Clin Experiment Ophthalmol* 2017;45(1):33–44.

SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amjmed.2020.07.013.

SEARCH STRATEGY AND STUDY SELECTION

Searches were carried out in PubMed and Embase from January 1, 2000 to January 1, 2020, using the following combination of search terms:

PUBMED (767)

((((((((((“myocardial ischemia”) OR myocardial ischemia) OR myocardial ischemia[MeSH Terms])) OR ((ischemic heart disease) OR ischemic heart disease[Title/Abstract])) OR (((acute coronary syndrome) OR acute coronary syndrome[Title/Abstract]) OR "acute coronary syndrome"[MeSH Terms])) OR (((((coronary atherosclerosis) OR "atherosclerosis"[MeSH Terms]) OR "coronary disease") OR "coronary artery disease"[MeSH Terms]) OR "coronary artery disease")) OR (((((((("heart failure") OR "heart failure"[MeSH Terms]) OR ventricular remodeling) OR "ventricular remodeling"[MeSH Terms]) OR heart valve diseases) OR heart valve diseases [MeSH Terms]) OR cardiomyopathies) OR cardiomyopathies[MeSH Terms])) OR (("Cardiac arrhythmias") OR Cardiac arrhythmias[MeSH Terms]))) AND ((((((retinal vessels[MeSH Terms]) OR "retinal vessels") OR retinal vessels[Title/Abstract]) OR retinal vessels OR retinal vascular diameter OR retinal vascular diameter OR retinal vascular tortuosity OR retinal arteriovenous nicking OR retina/arteriovenous ratio)) OR ((retina[MeSH Terms]) OR retinal signs))) AND ("2000/01/01"[PDAT]: "2020/01/01"[PDAT])) NOT (((((((rats) OR mouse) OR mice) OR piglet) OR animals)) AND (((((Diabetic retinopathy) OR "Diabetic retinopathy") OR "Diabetic retinopathy"[Title/Abstract]) OR hypertensive retinopathy) OR "hypertensive retinopathy") OR "hypertensive retinopathy"[Title/Abstract] AND ((((((((((((((((((((((((((((((case reports[Publication Type]) OR classical article[Publication Type]) OR clinical conference[Publication Type]) OR clinical study[Publication Type]) OR clinical trial[Publication Type]) OR Clinical Trial, Phase I [Publication Type]) OR Clinical Trial, Phase II[Publication Type]) OR Clinical Trial, Phase III[Publication Type]) OR Clinical Trial, Phase IV[Publication Type]) OR Comparative Study[Publication Type]) OR Consensus Development Conference[Publication Type]) OR Consensus Development Conference, NIH[Publication Type]) OR Controlled Clinical Trial[Publication Type]) OR Dataset[Publication Type]) OR English Abstract[Publication Type]) OR Evaluation Study[Publication Type]) OR Journal Article[Publication Type]) OR Guideline[Publication Type]) OR Historical Article[Publication Type]) OR Introductory Journal Article[Publication Type]) OR Meta-Analysis[Publication Type]) OR Multicenter Study[Publication Type]) OR News[Publication Type]) OR Newspaper Article[Publication Type]) OR Observational Study[Publication Type]) OR Practice Guideline[Publication Type]) OR Pragmatic Clinical Trial[Publication Type]) OR Randomized Controlled Trial[Publication Type]) OR Research Support, N I H, Extramural[Publication Type]) OR Review[Publication Type]) OR Scientific Integrity Review[Publication Type]) OR Technical Report[Publication Type]) OR Twin Study[Publication Type]) OR Validation Study[Publication Type]) OR Video-Audio Media[Publication Type]) OR Webcast[Publication Type]))

Embase (361)

(’retina’/exp OR ’retinal vascular disease’/kw OR ’retinal vascular caliber’/kw OR ’retinal vascular tortuosity’/kw OR ’retina blood vessel’/kw) AND (’ischemic heart disease’/kw OR ’acute coronary syndrome’/kw OR ’heart failure’/kw OR ’coronary artery disease’/kw OR ’heart arrythmia’/kw OR ’heart disease’/exp) AND [2000-2020]/py AND [english]/lim AND [article]/lim

SUPPLEMENTARY METHODS

Retinal Microvascular Signs

(a) Fluorescein angiography-derived signs:
   (I) arm-retina time, the time between administration of an opaque substance into the vein and its visibility in the retinal arteries;
   (II) arteriovenous passage time, the time between the entrance of the opaque substance to the edge of the optic disc or the retinal artery from a distance of 2 optic discs and the appearance of the opaque substance in the vein at the same point.

(b) OCTA-derived signs:
   (I) capillary flow density/capillary perfusion density, the area, expressed as the percentage occupied by the [area of the] vasculature for each of the following layers: retinal superficial capillary plexus, retinal deep capillary plexus, and choriocapillary layer.
   (II) capillary vessel density, the total length of perfused vasculature per unit area in the region of measurement.

Cardiac Imaging Studies for Evaluation of Coronary Artery Disease

The use of noninvasive imaging methods to depict the extent of coronary artery disease has become more popular over the years. Among the various available techniques, the two most commonly used are coronary computed tomography angiography (CCTA) and cardiac magnetic resonance imaging (MRI). Both have high negative predictive value in ruling out coronary artery disease, but are also useful in predicting clinical outcomes based on the extent of coronary atherosclerosis and on individual plaque characteristics.[1]

Another useful measurement is myocardial blood flow. Commonly calculated by cardiac MRI or single-photon emission computed tomography (SPECT), an isotopic marker is injected and its subsequent] perfusion during adenosine injection or cycle ergometry is compared with resting or normal mean values.[2]

A novel possibility is the use of intraluminal OCT, which allows direct visualization of coronary artery plaque during angiography.[3] OCT provides a detailed assessment of such plaque, including type (fibrotic, cholesterol, or calcific), thickness, length and arc angle.

Classifications of Coronary Artery Diseases

Coronary angiography is the gold standard for the diagnosis of coronary artery disease, and various classifications are used to depict its results.[4,5] The 5 classifications we used in our research were:

(I) The Gensini score, which scores narrowing of the lumen at the segmented progressively narrowing steps of 25%, 50%, 75%, 90%, 99%, and 100%. The score is then multiplied by a factor representing the relative amount of myocardium supplied by each segment.

(II) The Leaman score, which scores the narrowing of the lumen at each step of 70%, 90% 99%, and 100% narrowing. The score is then multiplied by the left ventricle (LV) weighing factor, which represents the vascular flow to the left ventricle (LV).

(III) The Extent score, which defines the proportion of the coronary arterial tree affected by angiographically detectable coronary atheroma. A formula is then used to calculate the proportion of the coronary artery intimal surface area] containing atheroma.[28]

(IV) The thrombolysis in myocardial infarction (TIMI) frame count, which uses an electronic frame counter. The TIMI frame count is defined as the number of cine-frames required for contrast to reach a standardized distal coronary landmark. Expression of the number is based on its relation to a normal cinefilming rate of 30 frames per second. a delay in the progression of the contrast injected into the coronary arteries is described as The coronary slow flow phenomenon.[7]

(V) Coronary artery calcification is measured by a coronary CT calcium scan and then calculated to obtain a coronary artery calcification score, which represents evidence of subclinical coronary artery disease and independently predicts future coronary events.[8]

SUPPLEMENTARY RESULTS

Retinal Microvascular Signs and Acute Coronary Syndrome

Research demographics. Out of the final total of 42 eligible studies, we chose 21 to test the association between retinal microvascular signs and acute coronary syndrome. Of these studies, 11 were prospective, 8 were cross-sectional, and 2 were retrospective. Retinal photographs with high-resolution digitized scanners had been used in 18 of those 21 studies (*Table* 1). Sample sizes ranged from 62 to 10,470, mean ages ranged from 60 to 79, and the proportion of male patients ranged from 37.9% to 100%. The parameter that had been most frequently examined in those studies for its association with acute coronary syndrome had been retinal vascular diameter.

Association with acute coronary syndrome. Kromer et al. found that CRAE, CRVE, AVR and acute coronary syndrome were not associated in patients who had experienced a myocardial infarction before the age of 50 or in age- and sex-matched healthy patients.[1] The EYE-MI OCTA Pilot study showed lower vascular and perfusion densities of the superficial capillary plexus in a group of patients presenting with acute coronary syndrome than in healthy patients. However, this association was not adjusted for cardiovascular disease risk factors, which were also found to be significantly associated with lower vascular density, making it difficult to isolate the relevant parameters needed for drawing conclusions [31]. In a recent study, spectral domain OCT showed that retinal arterial lumen diameter, retinal arterial outer diameter, and AVR were all lower in acute coronary syndrome patients presenting with both macrovascular and microvascular findings on angiography than in healthy controls.[3]

Retinal microvascular signs and coronary artery disease

Research demographics. A total of 14 cross-sectional studies were included in our research. Of these, retinal photographs with high-resolution digitized scanners had been used in 9, fluorescein angiography in 3, and OCTA in 3 (*Table* 2). Sample sizes ranged from 28 to 15,971, mean age from 49.5 to 70.2, and male proportion from 36.8% to 85%.

Retinal microvascular signs and coronary artery disease. In 2 studies fluorescein angiography was used to find positive correlations between armretina time, arteriovenous passage time, and angiography based Thrombolysis in Myocardial Infarction (TIMI) frame count.[32,11] In recent studies examining a possible correlation of OCTA with coronary artery disease, it was found that lower capillary vascular and flow densities in the different retinal layers were associated with coronary artery disease.[12,33]

Retinal microvascular signs and heart failure

Research demographics. A total of 10 studies, 2 of them prospective and 8 cross-sectional, were included in this section. Of the 10 studies, 9 used retinal photographs with high-resolution digitized scanners (Supplementary Table S2). The included studies were drawn from 3 cohorts: sample sizes ranged from 60 to 11,612; mean ages from 57 to 62.5, and male proportions from 35% to 75.5%. Retinal vascular diameter was the parameter most frequently examined for associations with acute coronary syndrome.

Retinal microvascular signs and heart failure. The two prospective studies included in this section were aimed at finding microvascular predictors of heart failure related hospitalizations or death based on the cohort of the Atherosclerosis Risk in Communities Study. After a mean follow

Supplementary Table S1 Risk Factors Used for Data Adjustment

	Author	Risk factors used for adjusted data
1	Wong (2002)[11]	Age, race, 6-year mean arterial blood pressure, diabetes, waist-hip ratio, sports index, total cholesterol, high density lipoprotein cholesterol, cigarette smoking, alcohol consumption, anti-hypertensive medication use.
2	McGeechan (2008)[12]	Race and Framingham variables (age, systolic blood pressure, total cholesterol, smoking status and HDL) and retinal venular caliber for models for arteriolar caliber (and vice versa).
3	Seidelmann (2016)[13]	Age, race, Systolic Blood Pressure, cigarette use, Total Cholesterol, HDL, DM, and hypertension medication.
4	Wang (2006)[14]	Age, systolic blood pressure, diabetes, smoking, venule-adjusted arteriolar caliber or arteriole-adjusted venular caliber.
5	Miller (2009)[15]	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
6	Liew (2019)[16]	Age, ethnicity, mean arterial pressure, diabetes, current smoking, body mass index, fellow eye vessel caliber, hypertension, stroke.
7	Wong (2006)[17]	Arteriolar caliber, venular caliber, age, gender, race, field center, systolic and diastolic blood pressure, diabetes status, glucose concentration, cigarette smoking status, pack-years of smoking, low-density-lipoprotein and high-density-lipoprotein cholesterol levels, body mass index, C-reactive protein level, internal carotid artery intima-media thickness.
8	Wang (2007)[18]	Age, gender, body mass index, hypertension, diabetes, serum total cholesterol, high density lipoprotein cholesterol, white blood cell count, and current smoking status, history of angina or acute myocardial infarct
9	Øhrn (2018)[19]	Age, gender, diabetes, hypertension, total serum cholesterol, use of cholesterol lowering drugs and current daily smoking.
10	Klein (2007)[20]	Age, gender, duration, glycosylated hemoglobin, systolic blood pressure, proteinuria, cardiovascular disease history, pack-years, diuretic use
11	Grunwald (2012)[21]	Age, gender, LDL, HDL, systolic blood pressure, smoking Status, diabetes, HYPERTENSION, Hemoglobin A1C, Triglycerides, eGFR, and log of 24H Urine Protein
12	Duncan (2002)[22]	Age, systolic and diastolic blood pressure, creatinine levels, and left ventricular hypertrophy score at baseline, total cholesterol, LDL-cholesterol, HDL-cholesterol, cholesterol treatment status, current or ex-smoking status, and fasting glucose levels at baseline.
13	Lam (2006)[23]	N/A
14	Liew (2010)[24]	Age, gender, body mass index, mean arterial blood pressure, smoking history, diabetes, history of CHD, white cell count, plasma fibrinogen, triglycerides, and HDL.
15	Wong (2003)[25]	Age and race
16	Wong (2002)[26]	Age, gender, income, history of cardiovascular disease, systolic blood pressure, antihypertensive medication use, diabetes, glycosylated hemoglobin, body mass index, cigarette smoking, and total and HDL cholesterol.
17	Kralev (2010)[27]	Age, gender, smoking, hypercholesterolemia, hypertension, obesity, family history of CAD, diabetes mellitus, prior myocardial infarction, previous angioplasty, previous bypass surgery, retinal microaneurysms and vasoconstriction.
18	Witt (2006)[28]	Age, gender, SBP, cholesterol, smoking status, antihypertensive therapy, HDL cholesterol, BMI, income.
19	Kromer (2018)[1]	N/A
20	Arnould (2018)[2]	N/A
21	Xu (2019)[3]	N/A
22	Kreis (2009)[4]	N/A
23	Cheng (2018)[5]	Age, gender, hypertension, diabetes, dyslipidemia, eGFR, diabetic retinopathy
24	Wong (2007)[6]	Age, gender, race/ethnicity, and study center, systolic blood pressure, antihypertensive medication, diabetes, serum glucose level, body mass index, total and high-density lipoprotein cholesterol level, triglyceride level, C-reactive protein level, current cigarette smoking, and pack-years of smoking, common carotid artery intima-media thickness, arteriolar caliber included additional adjustment for venular caliber and vice versa.
25	Josef (2013)[7]	Age, gender, smoking habits, metabolic syndrome, diabetes, BMI, and levels of ALT, HDL and LDL-cholesterol, triglycerides, and fasting glucose.
26	Gopinath (2014)[8]	Age, ethnicity, vessel caliber in the fellow eye, mean arterial blood pressure, body mass index, and presence of type 2 diabetes.
27	Wang (2008)[9]	Age, gender, and race/ethnicity, current smoking, hypertension, diabetes, systolic blood pressure, fasting blood glucose, low-density lipoprotein cholesterol, HDL cholesterol, and body mass index
28	Wightman (2019)[35]	N/A
29	Wang (2018)[34]	Age, gender, ethnicity, diabetes, BMI, systolic BP.
30	Koç (2013)[10]	Age, gender, hypertension, unstable angina, hemoglobin, low density lipoprotein, high density lipoprotein, smoking status.

Supplementary Table S1 (*Continued*)

	Author	Risk factors used for adjusted data
31	Taha (2018)[11]	N/A
32	Yang (2019)[12]	Age, gender, severity of diabetic retinopathy, dyslipidemia, coronary artery disease, hypertension, eGFR, hemoglobin A1c.
33	Wang (2019)[13]	N/A
34	Chandra (2019)[14]	Age, gender, race, body mass index, diabetes, use of anti-hypertensive medications, systolic blood pressure, current smoking, and current alcohol use.
35	Wong (2005)[15]	Age, gender, race, field center, educational levels, prevalent coronary heart disease, 6-year mean arterial blood pressure, use of antihypertensive medication, diabetes, glucose level, low-density lipoprotein cholesterol level, cigarette smoking, and body mass index.
36	Tikellis (2008)[16]	Age, gender, cardiovascular risk factors (serum total cholesterol, fasting glucose, diabetes, diabetes duration, smoking (never, former, current), BMI, waist-to-hip ratio, and exercise level) and hypertension-related factors (mean arterial blood pressure, antihypertensive medications use).
37	Meazza (2014)[17]	N/A
38	Cheung (2007)[18]	Age, gender, race (except race-stratified analysis), study center, pulse pressure, use of antihypertensive medications (except for hypertension-stratified analyses), diabetes, diabetes duration and glycosylated hemoglobin (except for diabetes-stratified analyses), body mass index, total and high-density lipoprotein cholesterol, triglycerides, cigarette smoking status, and C-reactive protein.
39	Chyou (2018)[19]	Age, gender, race/ethnicity, education, height, weight, and waist circumference, alcohol consumption, smoking (status and pack years), total cholesterol, HDL, hypertension, lipid-lowering medication, diabetes, hemoglobin A1c, and serum creatinine.
40	Phan (2015)[20]	Age, gender, body mass index (BMI), hypertension, diabetes mellitus, eGFR and smoking status.
41	Gopinath (2018)[21]	Age, gender, ethnicity, systolic blood pressure, body mass index, and presence of type 2 diabetes.
42	Chacko (2015)[22]	Age, gender, race, education, income, smoking, HDL and total cholesterol, hypertension status including hypertension medication use and diabetes status, C-reactive protein, peripheral artery disease, estimated glomerular filtration rate, anti-arrhythmic drug use, any major ECG abnormalities including left ventricular hypertrophy, baseline retinal venular caliber and baseline PR duration, incident cardiovascular disease.

Papers 1-18, 28,29 were cited from the manuscript; papers 19-27, 30-42 were cited from supplementary materials

up of 16 years, Chandra et al. reported that wider CRVE, narrower CRAE, and smaller AVR all adjusted for age, gender, and race, were significantly associated with incident heart failure. After further adjustment for clinical risk factors, however, only wider CRVE remained significant.[14] In the second prospective study, after a mean follow up period of 6.2 years, retinopathy, arteriovenous nicking and CRAE were found to be significantly associated with incident heart failure. However, Following further adjustment for clinical risk factors, only retinopathy remained significantly associated, while other signs showed only a trend.[15]

While the prospective cohorts mentioned in this section suggest only limited evidence for predictive ability of the vascular diameter for incident heart failure, stronger relationships between cardiac structural findings and heart failure were found in asymptomatic patients. In those patients, narrower CRAE was associated with left ventricular hypertrophy (LVH)[14,16,17] and with lower left ventricular (LV) diastolic and systolic functions including higher end-diastolic volume[14] and mass-to-volume ratio.[18] Wider CRVE was also associated with left ventricular hypertrophy (LVH) and lower ejection fraction.[14]

In one study, in which cardiac MRI was used to observe the right ventricle, and after adjusting for risk factors and left ventricular (LV) function, an association was found between wider CRVE and larger right ventricular end-diastolic mass and volume in women, Interestingly, wider CRVE was not associated with these variables in men, where it even showed inverse associations with right ventricular end-diastolic volume. The study's author suggested that in women, wider CRVE may reflect a general susceptibility to microvascular disease, as mentioned in the different chapters of our research. these changes may occur in the pulmonary veins and may therefore impose increased afterload on the right ventricle, as seen in the study's results. In the same study, narrower CRAE was associated with lower right ventricular end-diastolic mass and volume in both men and women.[19]

The Australian Heart Eye Study is a cross-sectional study in which the association of retinal microvascular structure with heart failure was examined on the basis of self-reported heart failure via questionnaires. Interestingly, retinal arteriolar widening, but not narrowing, was associated with prevalent heart failure. No association was found between venular diameter and heart failure.[20] This examination was later broadened for other retinal vascular parameters including Df, vascular tortuosity, and branching angle, none of which was found to be associated with heart failure.[21]

In the OCTA-based EYE-MI Pilot Study described in previous chapters, echocardiography indicated an association between lower vascular density and lower left ventricular (LV) ejection fraction[31]. However, the bias mentioned previously in that study was repeated, as only a bivariate analysis was used. The authors did not adjust the regression results for cardiovascular disease risk factors which were also found in the course of our research to be associated with lower vascular density.

Table S2 Retinal Vascular Signs Obtained by Fundus Photography and Its Associations with HF

S/N	Author	Cohort	Sample size	Demographics		Cardiac parameters observed	Retinal vascular parameters observed	Main result
				Age (mean years)	Male gender (%)			
Prospective studies								
1	Chandra (2019)[14]	Atherosclerosis Risk in Communities (ARIC) Study	N=10,692	60	35-52	Incident HF described as HF hospitalizations or death	CRAE, CRVE, AVR	Following a mean follow-up period of 16 years, Narrower CRAE and wider CRVE were associated with incident HF by 0.92 [CI 95% 0.87-0.97] and by (1.15 [CI 95% 1.09–1.20]), respectively per 1 standard deviation
2	Wong (2005)[15]	Atherosclerosis Risk in Communities (ARIC) Study	N=11,612	60	44-56	Incident HF described as HF hospitalizations or death	Retinopathy, arteriovenous nicking, focal arteriolar narrowing, CRAE	Following a mean follow up period of 6.2 years, retinopathy was associated with incident HF. (RR 1.96 [CI 95% [1.51-2.54]
Cross-sectional studies								
3	Chandra (2019)[14]	Atherosclerosis Risk in Communities (ARIC) Study	N=10,692	60	35-52	Structural and functional characteristics obtained by echocardiography	CRAE, CRVE	Narrower CRAE and wider CRVE were associated with LVH and worse diastolic and systolic function
6	Tikellis (2008)[16]	The Atherosclerosis Risk in Communities (ARIC) Study	N=1,439	57	36-38	Echocardiography LV measures	Focal narrowing, AV nicking, retinopathy, CRAE, CRVE	CRAE and focal narrowing were associated with LVH (OR 1.35 [95% CI 1.02–1.78], 1.66 [95% CI 1.16–2.38], respectively)
7	Meazza (2014)[17]	-	N=60	60.9	58.3	Echocardiography LV measures	CRAE, CRVE, AVR	Lower CRAE and AVR were associated with Left ventricular hypertrophy and remodeling
4	Cheung (2007)[18]	The Multi-Ethnic Study of Atherosclerosis (MESA)	N=4,593	-	-	LV mass index, volume index, and mass-to-volume ratio by cardiac MRI	CRAE, CRVE, Retinopathy	Narrower CRAE and retinopathy were associated with LV mass-to-volume ratio (OR 2.06, [95% CI 1.57 to 2.70], OR 1.31 [95% CI 1.08–1.61], respectively)
5	Chyou (2018)[19]	The Multi-Ethnic Study of Atherosclerosis (MESA)	N=3,630	62.5	48	RV end-diastolic volume and mass, end-systolic volume, stroke volume, ejection fraction by cardiac MRI	CRAE, CRVE	In women, wider CRVE was associated with larger RV end diastolic volume and mass. In both genders, narrower CRAE was associated with lower RV end diastolic volume and mass
8	Phan (2015)[20]	The Australian Heart Eye Study (AHES)	N=1,315	61.2-65.3**	70-75.5	HF prevalence by questionnaire	CRAE, CRVE	Wider CRAE was associated with prevalent HF
9	Gopinath (2018)[21]	The Australian Heart Eye Study	N=1,315	61.2-65.3**	70-75.5	HF prevalence by questionnaire	Df, curvature tortuosity and branching angle	None of the vascular geometric parameters were associated with prevalent HF

**ranges of means between different study groups.

Abbreviations: **OR**: Odds ratio, **CI**: Confidence interval; **AVR**: Arteriolar-venular ratio, **CRAE**: Central retinal artery equivalent, **CRVE**: Central retinal venous equivalent;; **Df**: Fractal dimension; **AV**: Arteriovenous; **HF**: Heart failure; **LV**: Left ventricle; **LVH**: Left ventricular hypertrophy; **MRI**: Magnetic resonance imaging; **RR**: Relative risk

Retinal Microvascular Signs and Conduction Abnormalities

Of the 3 studies included in this section, 2 were prospective and 1 was a cross-sectional study.

Chacko et al. looked for new atrioventricular conduction abnormalities by scrutinizing a cohort of patients who had participated in the Multi-Ethnic Study of Atherosclerosis, undergoing baseline fundus photography and electrocardiography, with a follow-up ECG a few years later. After a mean follow-up of 7.7 years, those authors found a significant association of narrower CRAE, but not of retinopathy, with any degree of arteriovenous block.[22]

In a prospective study of patients with chronic kidney disease, no association was found between retinopathy or retinal vascular diameter and atrial fibrillation or arrhythmia. That study, however, had some important limitations. Firstly, it specified that follow-up examinations were performed every 6 months, but did not indicate the length of the total follow-up period. Second, arrhythmia was not defined, and finally, the specific population and patient self-reported nature of outcome in this work are also a major limitation.[34]

In the Australian Heart Eye Study, a significant relationship was observed between the second Df tertile (but not the first or the third tertile) and the prevalence of atrial fibrillation. The odds of having atrial fibrillation were higher below a Df threshold of 1.472. However, the prevalence of atrial fibrillation was not related to vascular tortuosity or to branching angle.[21]

SUPPLEMENTARY DISCUSSION

OCTA is a relatively new technology that enables depth visualization of the retinal and choroidal capillary networks to study its vascular density and blood flow. This innovative diagnostic tool facilitates calculation of these signs in the superficial, deep, outer, and chorioicapillary layers. The studies on the use of this tool that are included in our research showed associations of lower vascular and perfusion density with acute coronary syndrome, coronary artery disease and lower left ventricular (LV) ejection fraction, with the caveat that some of those studies failed to adjust the results for cardiovascular disease risk factors. Their results seem promising, however, as the inner vessel density and flow could provide a more accurate prognostic and screening evaluation, and have already been shown to correlate with the REACH and GRACE scores for predicting acute coronary events.[31] Vessel histology can also be examined by OCT, as shown by one study in our research, where patients who manifested both macrovascular and microvascular acute coronary syndrome were found to have narrower arterial lumen and outer diameter, which were also associated with the extent of coronary artery disease. These results supported the evidence obtained from fundus photography studies mentioned above.

Our research has certain limitations. First, we excluded articles discussing solely the findings in patients with diabetic or hypertensive retinopathy. The main reason for this exclusion was that we wanted to focus our research on modern vascular measures rather than on the vastly explored measure of retinopathy. Another reason was that, as their names imply, these entities are well correlated in the literature with diabetes and hypertension, respectively; which in turn are correlated with cardiovascular diseases, including the cardiac diseases discussed in this article. Thus, this would constitute an inherent confounding factor. Another important limitation was that while most of the studies discussing acute coronary syndrome had defined their outcomes as a definite acute coronary syndrome with ST- or non-ST-elevation myocardial infarction or as an unstable angina event, a few studies had included patients who had undergone revascularization procedures, suggesting that those patients may not have experienced acute coronary syndrome but had undergone angiography for other reasons.[3,34–36]

REFERENCES

1. Kromer R, Tigges E, Rashed N, Pein I, Klemm M, Blankenberg S. Association between optical coherence tomography based retinal microvasculature characteristics and myocardial infarction in young men. *Sci Rep*. 2018;8(1):5615.
2. L. A, C. G, A. A, et al. The EYE-MI pilot study: a prospective acute coronary syndrome cohort evaluated with retinal optical coherence tomography angiography. *Investig Ophthalmol Vis Sci*. 2018;59(10):4299-4306. doi:10.1167/iovs.18-24090
3. Xu BL, Zhou WL, Zhu TP, et al. A full-width half-maximum method to assess retinal vascular structural changes in patients with ischemic heart disease and microvascular anginga. *Sci Rep*. 2019;9(1):11019. doi:10.1038/s41598-019-47194-5
4. Kreis AJ, Nguyen TT, Wang JJ, et al. Are retinal microvascular caliber changes associated with severity of coronary artery disease in symptomatic cardiac patients? *Microcirculation*. 2009;16(2):177-181.
5. Cheng L, Barlis P, Gibson J, et al. Microvascular retinopathy and angiographically-demonstrated coronary artery disease: A cross-sectional, observational study. *PLoS One*. 2018;13(5):e0192350.
6. Wong TY, Cheung N, Islam FMA, et al. Relation of retinopathy to coronary artery calcification: the multi-ethnic study of atherosclerosis. *Am J Epidemiol*. 2007;167(1):51-58.
7. Josef P, Ali I, Ariel P, Alon M, Nimer A. Relationship between retinal vascular caliber and coronary artery disease in patients with non-alcoholic fatty liver disease (NAFLD). *Int J Environ Res Public Health*. 2013;10 (8):3409-3423.
8. Gopinath B, Chiha J, Plant AJH, et al. Associations between retinal microvascular structure and the severity and extent of coronary artery disease. *Atherosclerosis*. 2014;236 (1):25e30. doi:10.1016/j.atherosclerosis.2014.06.018
9. Wang L, Wong TY, Sharrett AR, Klein R, Folsom AR, Jerosch-Herold M. Relationship between retinal arteriolar

narrowing and myocardial perfusion: multi-ethnic study of atherosclerosis. *Hypertension*. 2008;51(1):119-126.
10. Koç Ş, Ozin B, Altın C, Yaycıoğlu RA, Aydınalp A, Müderrisoglu H. Evaluation of circulation disorder in coronary slow flow by fundus fluorescein angiography. *Am J Cardiol*. 2013;111(11):1552-1556.
11. Taha NM, Asklany HT, Mahmoud AH, et al. Retinal fluorescein angiography: A sensitive and specific tool to predict coronary slow flow. *Egypt Hear J*. 2018;70(3):167-171.
12. Yang J, Wang E, Zhao X, et al. Optical coherence tomography angiography analysis of the choriocapillary layer in treatment-naïve diabetic eyes. *Graefe's Arch Clin Exp Ophthalmol*. 2019;257(7):1393-1399.
13. Wang X, Jiang X, Ren J. Blood vessel segmentation from fundus image by a cascade classification framework. *Pattern Recognit*. 2019;88:331-341.
14. Chandra A, Seidelmann SB, Claggett BL, et al. The association of retinal vessel calibres with heart failure and long-term alterations in cardiac structure and function: the Atherosclerosis Risk in Communities (ARIC) Study. *Eur J Heart Fail*. 2019.
15. Wong TY, Rosamond W, Chang PP, et al. Retinopathy and risk of congestive heart failure. *Jama*. 2005;293 (1):63-69.
16. Tikellis G, Arnett DK, Skelton TN, et al. Retinal arteriolar narrowing and left ventricular hypertrophy in African Americans. the Atherosclerosis Risk in Communities (ARIC) study. *Am J Hypertens*. 2008;21(3):352-359.
17. Meazza R, Scardino C, Grosso Di Palma L, et al. Target organ damage in hypertensive patients: correlation between retinal arteriovenular ratio and left ventricular geometric patterns. *J Hum Hypertens*. 2014;28(4):274-278. doi:10.1038/jhh.2013.69
18. Cheung N, Bluemke DA, Klein R, et al. Retinal arteriolar narrowing and left ventricular remodeling: the multi-ethnic study of atherosclerosis. *J Am Coll Cardiol*. 2007;50(1):48-55.
19. Chyou AC, Klein BEK, Klein R, et al. Retinal vascular changes and right ventricular structure and function: the MESA-Right Ventricle and MESA-Eye studies. *Pulm Circ*. 2018;9(1):2045894018819781.
20. Phan K, Mitchell P, Liew G, et al. Association between retinal arteriolar and venule calibre with prevalent heart failure: a cross-sectional study. *PLoS One*. 2015;10 (12):e0144850.
21. Gopinath B, Wang SB, Liew G, et al. Retinal Vascular Geometry and the Prevalence of Atrial Fibrillation and Heart Failure in a Clinic-Based Sample. *Hear Lung Circ*. 2018.
22. Chacko BG, Edwards MS, Sharrett AR, et al. Microvasculature and incident atrioventricular conduction abnormalities in the Multi-Ethnic Study of Atherosclerosis (MESA). *Vasc Med*. 2015;20(5):417-423.
23. Kohsaka S, Makaryus AN. Coronary angiography using noninvasive imaging techniques of cardiac CT and MRI. *Curr Cardiol Rev*. 2008;4(4):323-330.
24. de Jong MC, Genders TSS, van Geuns R-J, Moelker A, Hunink MGM. Diagnostic performance of stress myocardial perfusion imaging for coronary artery disease: a systematic review and meta-analysis. *Eur Radiol*. 2012;22 (9):1881-1895.
25. Yoon JH, Di LV, Moses JW, et al. Feasibility and safety of the second-generation, frequency domain optical coherence tomography (FD-OCT): a multicenter study. *J Invasive Cardiol*. 2012;24(5):206-209.
26. Knudtson M. Coronary scoring systems. *A Hist Perspect*. 2014.
27. Neeland IJ, Patel RS, Eshtehardi P, et al. Coronary angiographic scoring systems: an evaluation of their equivalence and validity. *Am Heart J*. 2012;164(4):547-552.
28. Sullivan DR, Marwick TH, Freedman SB. A new method of scoring coronary angiograms to reflect extent of coronary atherosclerosis and improve correlation with major risk factors. *Am Heart J*. 1990;119 (6):1262-1267. doi:10.1016/s0002-8703(05)80173-5
29. Gibson CM, Cannon CP, Daley WL, et al. TIMI frame count: a quantitative method of assessing coronary artery flow. *Circulation*. 1996;93(5):879-888.
30. Bamberg F, Sommer WH, Hoffmann V, et al. Meta-analysis and systematic review of the long-term predictive value of assessment of coronary atherosclerosis by contrast-enhanced coronary computed tomography angiography. *J Am Coll Cardiol*. 2011;57(24):2426-2436.
31. Arnould L, Guenancia C, Azemar A, et al. The EYE-MI pilot study: a prospective acute coronary syndrome cohort evaluated with retinal optical coherence tomography angiography. *Invest Ophthalmol Vis Sci*. 2018;59 (10):4299-4306.
32. Koc S, Ozin B, Altin C, Altan Yaycioglu R, Aydinalp A, Muderrisoglu H. Evaluation of circulation disorder in coronary slow flow by fundus fluorescein angiography. *Am J Cardiol*. 2013;111(11):1552-1556. doi:10.1016/j.amjcard.2013.01.324
33. Wang J, Jiang J, Zhang Y, Qian YW, Zhang JF, Wang ZL. Retinal and choroidal vascular changes in coronary heart disease: an optical coherence tomography angiography study. *Biomed Opt Express*. 2019;10(4):1532-1544.
34. Grunwald JE, Ying G-S, Maguire M, et al. Association between retinopathy and cardiovascular disease in patients with chronic kidney disease (from the Chronic Renal Insufficiency Cohort [CRIC] Study). *Am J Cardiol*. 2012;110(2):246-253.
35. Wong TY, Klein R, Sharrett AR, et al. Retinal arteriolar narrowing and risk of coronary heart disease in men and women: the Atherosclerosis Risk in Communities Study. *Jama*. 2002;287(9):1153-1159.
36. Miller RG, Prince CT, Klein R, Orchard TJ. Retinal vessel diameter and the incidence of coronary artery disease in type 1 diabetes. *Am J Ophthalmol*. 2009;147 (4):653-660.