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EVIDENCE-BASED MEDICINE, CLINICAL TRIALS AND THEIR INTERPRETATIONS (L. ROEVER, SECTION EDITOR)

Association Between Caliber of Retinal Vessels and Cardiovascular Disease: a Systematic Review and Meta-Analysis

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Abstract

Purpose of Review The aim of this study to is report the findings of a systemic review and meta-analysis of the literature on the association between retinal vascular caliber and cardiovascular diseases.

Recent Findings The caliber of retinal vessels has been recognized as an important biomarker for risk stratification in various cardiovascular diseases, such as coronary artery disease, heart failure, stroke, and mortality.

Summary Non-invasively quantifying retinal vasculature may be useful in screening individuals who are at risk of cardiovascular disease. Further evaluating the role of retinal vessel anatomy and incorporating it into a scoring system on risk of cardiovascular diseases are needed in future studies.

Keywords Retinal vessel · Cardiovascular diseases · Coronary artery disease · Heart failure · Stroke · Mortality

Introduction

Cardiovascular diseases remain a leading cause of morbidity and mortality globally, placing a significant economic and societal burden despite advances in prevention, diagnosis, and therapy. Although many risk factors of cardiovascular disease, such as hypertension, diabetes mellitus, hyperlipidemia, smoking, and obesity, have been reported, their pathophysiology is diverse and there remains a need to identify useful biomarkers for early diagnosis and risk stratification.

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Topical Collection on *Evidence-Based Medicine, Clinical Trials and Their Interpretations*

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Cardiovascular diseases are characterized by generalized systemic inflammation accompanied by abnormalities in the microcirculation of different organs and tissues. Importantly, the retinal vasculature in the eye is the only microcirculation that can be observed non-invasively. In recent years, there have been numerous studies that assessed the relationship between the caliber of retinal vessels and coronary artery disease, heart failure, stroke, and mortality [1••, 2••, 3]. Seidelmann et al. found that narrowing of the retinal arterioles and widening of venules were associated with higher long-term mortality in both genders [2••]. By contrast, Wong et al. conducted a prospective cohort study demonstrating no significant relationship between the diameter of retinal arterioles or venules, or between the arteriole-to-venule ratio and mortality [4]. Therefore, we performed an extensive search in the databases of PubMed, EMBASE, and Cochrane library to identify studies that showed association between cardiovascular disease and retinal vascular disease.

Methods

Search Strategy

This systematic review and meta-analysis was conducted according to the preferred reporting items in systematic review and meta-analysis (PRISMA) statement [5]. Two investigators independently reviewed the literature to identify all studies that describe retinal vascular signs such as retinal vessel caliber, focal retinal arteriolar narrowing, arteriovenous nicking, and incidence of cardiovascular disease in PubMed, EMBASE, and Cochrane library. Entries published up to the 17th July, 2019, were searched. The search terms used were retinal vessels (MeSH), retinal blood vessel, retinal artery, retinal vein, retinal microvascular, retinal arteriolar, retinal venous, retinal vascular, arteriolar narrowing, arteriovenous nicking, arteriovenous nicking, venular dilation, venular dilatation, venular dilatation arterio-venular ratio, focal arterio-venular narrowing, generalized arteriolar narrowing, flicker light–induced retinal arteriolar dilation, flicker light–induced retinal venular dilation and cardiovascular diseases(MeSH), heart failure, coronary artery disease, ischemic heart disease, stroke, cerebrovascular disease, apoplexy, transient ischemic attack, heart disease, mortality.

Selection Criteria

Publications that met the following criteria were included in meta-analysis: (1) prospective cohort studies; (2) conducted in general population; (3) reported retinal vascular caliber either photographic film or digital photographs using computer-associated methods; (4) reported incidence of cardiovascular disease as endpoint with a description of RRs or HRs. For systematic review, the inclusion criteria were reported association of cardiovascular disease with retinal vessel feature such as vascular caliber changes, arteriovenous nicking, and flicker light–induced retinal vascular dilation. The search procedure was performed by two reviewers (SG and SY). Discrepancies were resolved by consensus or, if necessary, by a third author (TL).

Data Extraction

Two reviewers (SG and SY) extracted relevant data from each eligible article independently and subsequently their extraction were cross-checked. The standard data extraction form included the characteristics of studies and baseline characteristics of included patients. Information on publication year, retinal feature, sample size, study design, incidence of cardiovascular disease, mean age, female ratio, follow-up duration, and risk estimate.

Statistical Analysis

All data analysis was performed by using Review Manager (Version 5.3). The magnitude of association between incidence of cardiovascular disease and retinal vascular calibers was represented by hazard ratios (HRs). We used the inverse variance method to weight studies for the combined overall statistic. Heterogeneity between studies was evaluated by the I^2 statistic. If I^2 value > 50%, which reflected significant heterogeneity, the random effects model was used; otherwise, the fixed effects model was used.

Results

A total of 29,540 articles were identified initially (Fig. 1). Of these, 7546 duplicates and 21,775 based on title and abstract were excluded. Subsequently, 185 articles were excluded because they did not provide measures that reported the association between these retinal vessel caliber and cardiovascular disease risk were editorials or not published in English. Finally, a total of 34 articles were included in this study and their characteristics are summarized in Table 1. Among these articles, 11 studies were investigating coronary artery disease, 5 studied heart failure, 12 studied stroke, and 6 studied mortality.

Coronary Heart Disease

Previous studies suggested that retinal vascular diameters are related to various cardiovascular risk factors such as atherosclerosis, inflammation, and cholesterol levels [31] in diseases such as hypertension [32], diabetes [33], and metabolic syndrome [34]. Narrowing of retinal arterioles has been associated with a lower hyperemic myocardial blood flow and perfusion reserve [35]. Moreover, in patients with high grade hypertensive retinopathy, myocardial perfusion was impaired [36]. The explanation is likely systemic inflammation that causes atherosclerosis of the coronary vasculature is also responsible for alterations in structure and function of retinal vessels [37]. Over the recent years, a computer-assisted digital method of quantifying retinal vessel anatomy has emerged, which can indirectly assess the coronary microcirculation. Indeed, a narrower retinal arteriolar caliber and a wider retinal venular caliber are reported to predict the risk [11•, 15•]. Moreover, retinal microvascular abnormities can be used as a marker of CAD severity [8]. Thus, retinal venular caliber was increased in triple vessel disease [7], and atherosclerosis of retinal vessels was a significant predictor of coronary atherosclerosis [38]. A less dense retinal microvascular network, represented by a lower fractal dimension, and a narrower arteriolar branching angle have been associated with increasing CAD vessel score [39]. However, other studies failed to demonstrate significant predictive values of retinal atherosclerosis. These results are not consistent. Prospective studies based on general population found stronger associations in women, with weaker or no association in men [11•, 14]. There was also a lack of predictive value in type 1 diabetic patients [13], findings that were confirmed by a subsequent meta-analysis [12]. Recently, a prospective study by Seidelmann et al. [2••] did not find a significant association of retinal vessel changes with CAD. In support of this, data from several

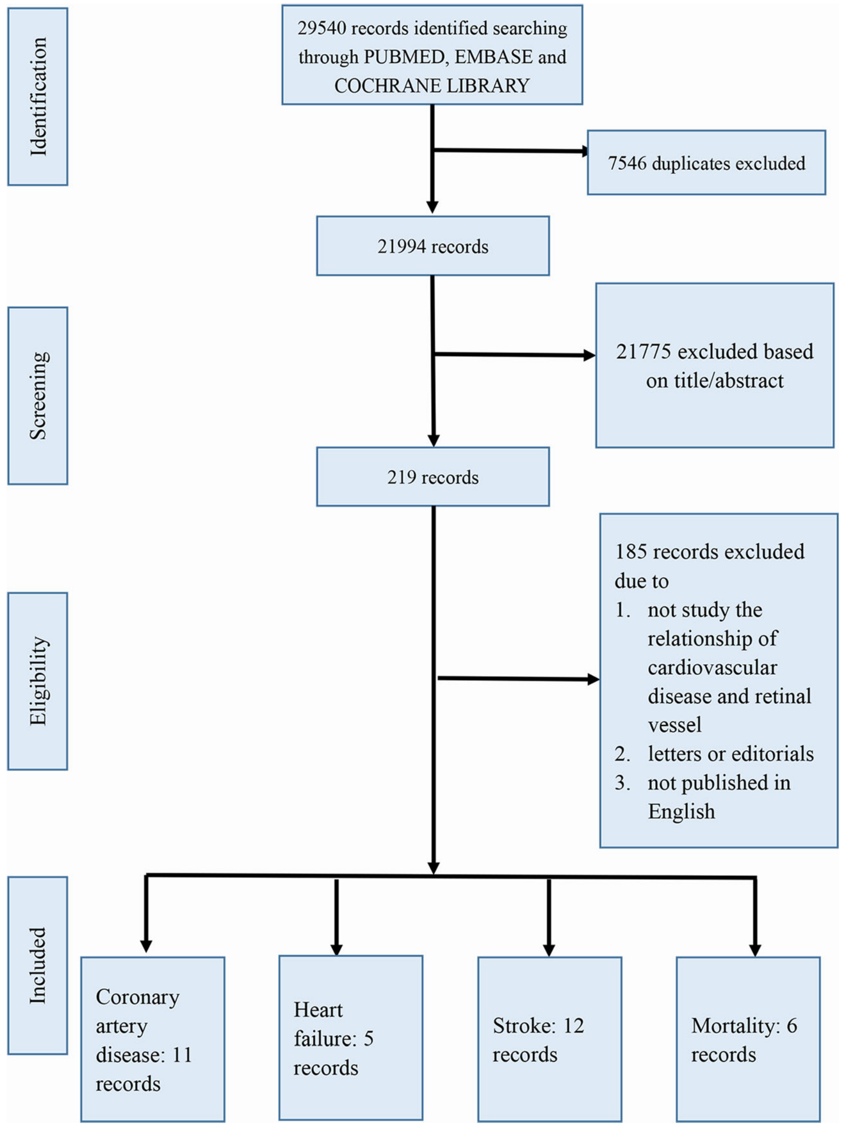

Fig. 1 A PRISMA flow diagram of this study

cross-sectional and case–control studies only found weaker associations between alterations in retinal vessels and CAD severity [9, 10]. Al-Fiadh et al. demonstrated that flicker light–induced dilatation of the retinal arterioles, but not the caliber of retinal arterioles or venules, is an independent predictor of CAD [6••]. These findings therefore demonstrate that perhaps both the anatomy and physiological functionality of retinal vessels are important for risk stratification in CAD.

Heart Failure

Heart failure is a significant problem associated with a higher morbidity, mortality, increased hospitalizations, in-hospital length of stay, and a poorer quality of life. Endothelial dysfunction of the coronary and systemic vasculature plays an important role in pathogenesis of heart failure [40]. However, only a few studies have been conducted to explore the roles of endothelial dysfunction of the retinal microcirculation for risk prediction in heart failure. Prior reports have suggested that adults with retinal arteriolar narrowing were more likely to have left ventricular hypertrophy and cardiac remodeling [41, 42]. In 2015, a cross-sectional study involving 1680 participants found a significant association between wider caliber of retinal venules and prevalent heart failure [18]. While, in 2018, an updated view was put forward as no difference in retinal vascular caliber was found between groups of participants with chronic heart failure, cardiovascular risk factors, and healthy controls [1••]. However, as with CAD, retinal microvascular dilatation induced by flicker light is impaired in chronic heart failure patients [1••]. Additionally, Barthelmes et al. [43] demonstrated significant impairment of the endothelial function of retinal arteries in heart failure patients with either preserved or reduced ejection fraction.

The ARIC study (The Atherosclerosis Risk in Communities Study) published in 2016 did not find a significant association

Table 1 Resume of studies on the association between retinal vascular abnormalities and cardiovascular disease

Study	Year	Retinal feature	Study type	No. of participants	Incidence rate (%)
1. Coronary artery disease					
Al-Fiadh [6••]	2015	RAC; RVC; FIDart	Case–control	Case: 78 Control: 119	–
Cheng [7]	2016	RAC; RVC	Cross-sectional	144	–
Gopinath [8]	2014	RAC; RVC	Cross-sectional	991	–
Kralev [9]	2010	AVR	Case–control	ACS: 23 Stable CAD: 19	–
Kreis [10]	2009	RAC; RVC	Cross-sectional	98	–
McGeechan [11•]	2008	RAC; RVC	Prospective cohort	9155	7.6
McGeechan [12]	2009	RAC; RVC	Meta-analysis	22,159	10
Miller [13]	2009	RAC; RVC	Prospective cohort	Type 1 DM: 448	17.9
Seidelmann [2••]	2016	RAC; RVC	Prospective cohort	10,470	13.3
Wong [14]	2002	AVR	Prospective cohort	9648	2.8
Wong [15•]	2006	RAC; RVC	Prospective cohort	1992	5.8
2. Heart failure					
Chandra [16••]	2019	RAC; RVC	Prospective cohort (ARIC)	10,629	14.6
Gopinath [17]	2018	Df; arteriolar tortuosity; venular tortuosity;	Case–control	Case: 62 Control: 832	–
Nägele [1••]	2018	RAC; RVC; AVR; FIDart	Case–control	HF: 74 CVRF: 74 Control: 74	–
Phan [18]	2015	RAC; RVC	Cross-sectional	1680	6.4
Seidelmann [2••]	2016	RAC; RVC	Prospective cohort (ARIC)	10,470	13.3
3. Stoke					
Cheung [19]	2013	RAC; RVC; Df; arteriolar tortuosity; venular tortuosity	Prospective cohort	3189	1.6
Cooper [20]	2006	Arteriovenous nicking; arteriolar narrowing; AVR	Cross-sectional	1684	9.4
Dumitrascu [21]	2018	Retinal arteriole narrowing; diabetic retinopathy; retinal arteriovenous nicking; retinal hemorrhage;	Meta-analysis	56,370	–

Table 1 (continued)

		retinal microaneurysm; retinal fractals			
Kawasaki [22]	2011	Df	Case–control	Case: 101 Control: 184	–
Kawasaki [23]	2012	RAC; RVC	Prospective cohort	4849	1.3
McGeechan [24•]	2009	RAC; RVC	Meta-analysis	20,798	4.5
Ong	2013	Df	Case–control	Case: 557 Control: 557	–
Seidelmann [2••]	2016	RAC; RVC	Prospective cohort	10,470	5.2
Wieberdink [25]	2010	RAC; RVC	Prospective cohort	5528	11.3
Wong [15•]	2006	RAC; RVC	Prospective cohort	1992	5.7
Wu [26]	2017	Retinal arteriole narrowing; diabetic detinopathy; retinal arteriovenous nicking; retinal hemorrhage; retinal microaneurysm; retinal fractals	Meta-analysis	20,659	5.7
Yatsuya	2010	RAC; RVC; focal arteriolar narrowing; arteriovenous nicking; retinopathy signs	Prospective cohort	10,496	3.2%
1. Mortality					
Arnould [27]	2018	Sparse vascular network;	Cross-sectional	1069	–
Roy [28]	2012	RAC; RVC	Prospective cohort	Type 1 DM: 468	21.8
Seidelmann [2••]	2016	RAC; RVC	Prospective cohort	10,470	26.7
Wang [29]	2007	RAC; RVC	Prospective cohort	7494	CHD death: 8.7 Stroke death: 3.1
Wong [30]	2003	AVR; focal arteriolar narrowing; arteriovenous nicking	Case–control	1611	25.6
Wong [4]	2004	RAC; RVC; AVR	Prospective cohort	4926	24.3

Study	Mean age	Female ratio (%)	Follow-up years	Risk estimate	Results	Whether included into meta-analysis
1. Coronary artery disease						
Al-Fiadh [6••]	Case: 63 Control: 55	Case: 18 Control: 45	–	Mean (SD)	FIDart is an independent predictor of the presence of CAD. RAC and RVC are not associated with CAD.	No
Cheng [7]	61	30	–	Mean (SD)	Venular caliber was increased with triple vessel disease	No

Table 1 (continued)

Gopinath [8]	60.2	25.4	–	ORs (by quintile of retinal vessel caliber)	Narrower RAC and wider RAC were associated with more diffuse and severe CAD among women.	No
Kralev [9]	ACS: 63.4 Stable CAD: 65.4	ACS: 33 Stable CAD: 26	–	ORs	There is no difference in AVR between groups.	No
Kreis [10]	64	-Resume	–	Mean (SD)	Retinal vascular caliber changes are not associated with the severity of obstructive CAD.	No
McGeechan [11•]	59.4	58.2	8.8	HRs (per-SD change)	Narrower RAC and wider RAC are related to risk of CHD in women but not in men.	No
McGeechan [12]	62	59	4–15	HRs (per-SD change)	Narrower RAC and wider RVC were associated with an increased risk of coronary heart disease only in women.	No
Miller [13]	25.4	50.7	18	HRs (per-SD change)	Narrower RAC may indicate an increased risk of CAD in women, but not men, with T1D.	No
Seidelmann [2••]	59.5	56.8	16	HRs (per-SD change)	No significant association of narrower RAC and wider RVC with CHD was found.	No
Wong [14]	51–72	57.9	3.5	RRs (by quintile of retinal vessel caliber and per-SD change)	Narrower RAC is related to risk of CHD in women but not in men.	No
Wong [15•]	69–97	NA	5	RRs (by quintile of retinal vessel caliber)	Narrower RAC and wider RVC were associated with an increased risk of coronary heart disease.	No
2. Heart failure						
Chandra [16••]	60	56	16	HRs (per-SD change)	Retinal vessel caliber imaging, which characterizes retinal microvasculature, is a simple, non-invasive test that predicts incident HF and adverse cardiac structure/function.	No
Gopinath [17]	Case: 65.2 Control: 60.5	Case: 32.3 Control: 24.8	–	ORs (by quintile of retinal vessel caliber)	Retinal vascular geometric variables were also not associated with prevalence of heart failure.	No
Nägele [1••]	HF: 63.5 CVRF: 64.1 Control: 57.8	HF: 32 CVRF: 34 Control: 35	–	Mean (SD)	FIDart is impaired in HF, No difference in RAC and RVC was found between groups.	No
Phan [18]	61.6	24.9	–	OR (by quintile of retinal vessel caliber)	Wider RVC was significantly associated with prevalent heart failure.	No
Seidelmann [2••]	59.5	56.8	16	HRs (per-SD change)		No

Table 1 (continued)

					No significant association of narrower RAC and wider RVC with heart failure was found.	
3. Stoke						
Cheung [19]	40–80	NA	4.41	HRs (by quintile of retinal vessel caliber)	Wider retinal venular caliber is related to an increased risk of stroke.	Yes
Cooper [20]	62.2	59.8	–	ORs	Retinal microvascular abnormalities are associated with MRI-defined subclinical cerebral infarcts independent of stroke risk factors.	No
Dumitrascu [21]	–	–	3.3–20	ORs	Focal arteriolar narrowing and retinopathy predicted cerebrovascular ischemic diseases subtypes after risk factor adjustment	No
Kawasaki [22]	73.	58	–	ORs (by quintile of retinal vessel caliber and per-SD change)	Low Df of retinal vasculature was associated with twofold higher risk of incident stroke events compared with persons with high Df.	No
Kawasaki [23]	62.5	53	6	HRs (by quintile of retinal vessel caliber)	Narrower RAC in non-diabetic persons were associated with increased risk of stroke.	Yes
McGeechan [24•]	–	–	5–12	HRs (per 20-um increase in caliber)	Inclusion of retinal venular caliber in prediction models containing traditional stroke risk factors reassigned 10.1% of people at intermediate risk into different risk categories.	No
Ong	61.9	63.9	–	ORs	Patients with ischemic stroke have a sparser and more tortuous microvascular network in the retina.	No
Seidelmann [2••]	59.5	56.8	16	HRs (per-SD change)	Narrower RAC and wider RVC conferred long-term risk of ischemic stroke in both sexes.	Yes
Wieberdink [25]	67.8	59.1	11.5	HRs (by quintile of retinal vessel caliber and per-SD change)	Wider RVC is associated with an increased risk for stroke in the general population and, in particular, with intracerebral hemorrhage.	Yes
Wong [15•]	69–97	NA	5	RRs (by quintile of retinal vessel caliber)	Wider RVC is independently associated with risk of stroke in elderly persons.	Yes
Wu [26]	–	–	–	ORs	Retinal vasculature changes have a specific relationship to stroke.	No

Table 1 (continued)

Yatsuya	59	56	11.2	HRs (per-SD change)	1. Narrower RAC, wider RVC, focal arteriolar narrowing, and arteriovenous nicking were predictive of lacunar stroke but not other ischemic stroke subtypes.	No
1. Mortality						
Arnould [27]	80	63.2	–	Median (IQR)	The Sparse vascular network pattern was associated with a higher risk profile for cardiovascular mortality risk at 10 years.	No
Roy [28]	NA	NA	6	ORs	Narrower RAC, not wider RVC, was associated with an increased risk of mortality in type 1 diabetes.	No
Seidelmann [2••]	59.5	56.8	16	HRs (per-SD change)	Narrower RAC and wider RV conferred long-term risk of mortality in both sexes.	No
Wang [29]	62.9	55.9	10–12	HRs (by quintile of retinal vessel caliber)	Narrower RAC and wider RVC were also associated with an increased risk of CHD-mortality and stroke-mortality among persons aged 43–69.	No
Wong [30]	43–84	Case: 46.7 Control: 49.2	–	ORs	Focal arteriolar narrowing, arteriovenous nicking, and AVR were only associated with cardiovascular mortality in middle-aged persons(43 to 75 years)	No
Wong [4]	61.9	55.8	10	HRs (by quintile of retinal vessel caliber)	No significant association of narrower RAC and wider RVC with mortality was found.	No

ACS, acute coronary syndrome; *AVR*, arterio-venular ratio; *CAD*, coronary artery disease; *CHD*, coronary heart disease; *Df*, fractal dimension; *FIDart*, flicker light–induced retinal arteriolar dilation; *HR*, hazard ratio; *RR*, risk ratio; *OR*, odds ratio; *HR*, hazard ratio; *RAC*, retinal arteriolar caliber; *RVC*, retinal venular caliber; *SD* standard deviation; *T1D* type 1 diabetes mellitus between retinal vessel caliber and heart failure [2••], findings that are supported by findings in a clinic-based sample of heart failure patients [17]. Surprisingly, later evidence by the ARIC study group published in 2019 found that the caliber of retinal vessels predicted incident heart failure, increased left ventricular size, higher incidence of left ventricular hypertrophy, and greater abnormalities in diastolic and systolic function [16••]. These discrepancies between the 2016 and 2019 findings may be due to the length of follow-up, with retinal vessel anatomy only demonstrating predictive value over longer time periods.

Stroke

Stroke is a debilitating disease leading to poor functionality and quality of life. Although many important risk factors have been identified, early biomarkers for stroke are still required. There is increasing evidence that change of retinal microcirculation can be a marker of stroke, given that retinal and cerebral vessels share embryologic, anatomic, and physiologic similarity [44–46]. Thus, non-invasive examination of the retina can provide useful information for physicians to risk stratify their patients.

The ARIC study published in 2016 found that a narrower retinal arteriolar caliber and a wider retinal venular caliber were associated with a higher risk of stroke in both genders in the long term [2••]. By contrast, prior prospective studies found that only a wider retinal venular caliber independently predicted a higher stroke risk [15•, 23, 25], as confirmed by a previous meta-analysis conducted in 2009 [24•]. Given such discrepancies, we performed a meta-analysis to further explore the relationship between stroke and retinal vessel caliber change. In our analysis, a total of 5 studies [2••, 15•, 19, 23, 25]. Grouping of studies were by either quantiles of retinal vessel caliber (fifth vs. first quartile for retinal vein; first vs. fifth quartile for retinal artery) or per-standard deviation (SD) change. In both analyses, both narrower retinal arteriolar caliber and wider retinal venular caliber were predictive of long-term incidence of stroke in general population. The hazard ratios were 1.4 (95% CI 1.11–1.77, $P = 0.005$; Fig. 2a) for arteriolar caliber and 2.45 (95% CI 1.5–4.0; $P = 0.0003$; Fig. 2b) for venular caliber in quintiles, and 1.14 (95% CI 1.05–1.23, $P = 0.0009$; Fig. 2c) and 1.20 (95% CI 1.12–1.28, $P < 0.00001$; Fig. 2d), respectively, for per-SD change.

Finally, patients with ischemic stroke have a sparser and more tortuous microvascular network (lower fractal dimension) in the retina, and a lower fractal dimension was associated with a twofold higher risk of incident stroke [22]. Other retinal microvascular abnormal signs, including arteriovenous nicking, smaller arterio-venular ratio, retinal microaneurysm, and focal arteriolar narrowing, have also been found to be

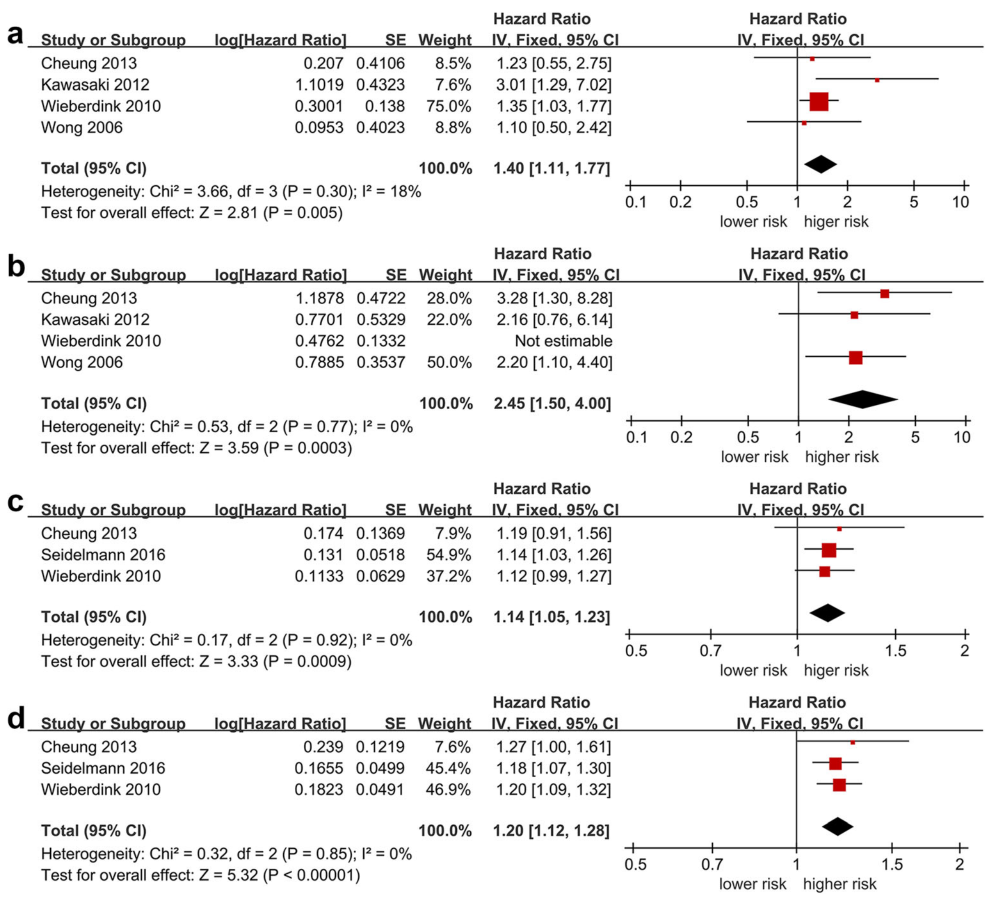

Fig. 2 Forest plots of the hazard ratio (HRs) for stroke events by comparing smallest quartile with largest quartile of retinal arteriolar caliber (**a**), or largest quartile with smallest quartile of retinal arteriolar caliber (**b**), or by per-standard deviation (SD) change of retinal vessel caliber (**c**, **d**)

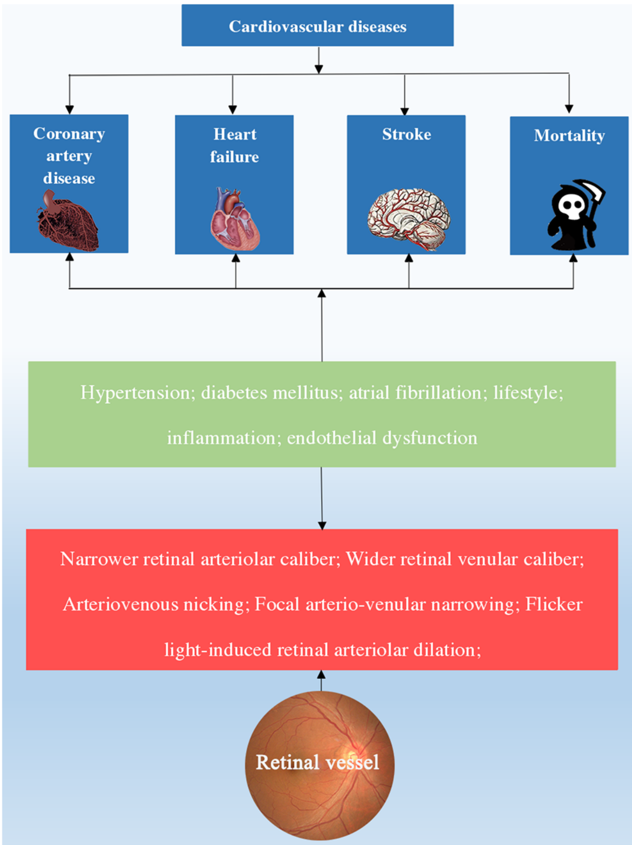

Fig. 3 Summary diagram detailing the relationship between retinal vascular abnormalities and pathogenesis of various cardiovascular diseases

helpful markers of stroke events [20, 21, 26]. Risk prediction models involving retinal vessel characteristics may improve the accuracy for predicting recurrence of stroke [47].

Mortality

The association between caliber of retinal vessels at baseline and mortality has been controversial. Prior studies have reported that retinal microvascular disease was associated with a higher cause-specific but not necessarily all-cause mortality [30, 37]. The ARIC study [2••] concluded that both narrower retinal arteriolar caliber and wider retinal venular caliber were significantly contributed to the higher risk of all-cause death, while studies conducted by Wang et al. [29] and Wong et al. [30] indicated that alterations in the anatomy or structure of retinal vessels (including narrower retinal arteriolar caliber, wider retinal venular caliber, arterio-venular ratio, focal arteriolar narrowing, and arteriovenous nicking) were associated with higher mortality only in the middle-aged population. Arnould et al. further reported that a sparse vascular network pattern was associated with a higher cardiovascular mortality risk at 10 years [27]. Retinal arteriolar caliber has been shown to be a better predictor of mortality than retinal venular caliber in type 1 diabetic patients [28]. By contrast, Wong et al. [4] did not demonstrate a significant predictive value for retinal vessel variables. Thus, more prospective studies are needed to determine the value of retinal vascular abnormalities for mortality risk stratification.

Discussion

To the best of our knowledge, this is the first systematic review and meta-analysis reporting on the association between retinal vascular caliber and cardiovascular disease. Different from the previous meta-analysis on retinal vessel caliber and stroke [24•], our meta-analysis, including more recent studies tend to support that both retinal arteriolar and venous caliber, is associated with stroke. The main findings are that structural and functional abnormalities in the retinal microcirculation can be used to predict cardiovascular disease incidence and adverse outcomes (Central Illustration Figure; Fig. 3). This ability stems from the fact that similar risk factors or comorbidities are found for retinal vascular abnormalities and cardiovascular disease. These include hypertension, diabetes, atrial fibrillation, and a sedentary lifestyle.

For hypertension, a retrospective study conducted by Daugherty et al. analyzed data from 18,036 patients, and at 4-year follow-up, resistant hypertension was associated with an increased risk of adverse cardiovascular outcomes on multivariable Cox regression analysis [48]. The mechanism is traditionally explained as that hypertension could lead to diastolic dysfunction and concentric left ventricular hypertrophy, and if pressure overload is sustained, further cardiac dysfunction would ensue, which would culminate in poor outcomes [49]. Additionally, arterial stiffness, caused by hypertension [50], can transmit greater pulsatile energy to the microcirculation, which may lead to peripheral end-organ damage [51, 52].

Type 2 diabetes is an independent risk factor of cardiovascular events, atrial fibrillation (AF), and cardiovascular mortality [53]. It can induce adverse remodeling of blood vessels including those from the retina [54]. A cross-sectional study analyzing 1680 participants has shown that a sparser retinal microvascular network was independently associated with a higher likelihood of incident AF [17]. Finally, a healthy lifestyle has a powerful effect in reducing the risk of developing age-related chronic diseases [55], and has similarly shown protective effects on the retinal microvascular health [56, 57]. Chronic inflammation, which is exacerbated by aging, leading to endothelial dysfunction, is responsible for the pathogenesis of many cardiovascular disorders [58, 59]. Activation of pro-inflammatory pathways is likely to be responsible for inducing abnormalities in the retinal vasculature [60, 61].

Limitations

Several limitations of this study should be noted. Firstly, this meta-analysis included observational studies and can be susceptible to some types of studies inherent in this type of studies. Secondly, the gender and age distribution were not uniform across different groups. Finally, incidence of stroke varies significantly among the studies, which might have unpredictable effects on estimates of risk.

Future Directions

Despite the significant discrepancy on the issue that whether retinal anatomy and function are associated with cardiovascular disease, published data of long-term follow-up in recent years have demonstrated promising results. Retinal photography can be used as a screening tool. Future prospective studies should explore the value of retinal photography for screening and quantifying cardiovascular risk in the general population.

Conclusion

This is a systematic review and meta-analysis on studies reporting associations between alterations in retinal vasculature in coronary artery disease, heart failure, stroke, and mortality. Our meta-analysis including more recent studies supports the notion that calibers of both retinal arteriolar and venous vessels are associated with stroke. Together, a multi-parametric score incorporating retinal-specific abnormalities and systemic cardiovascular risk factors would likely to improve risk stratification of cardiovascular diseases among individuals. Non-invasive methods of quantifying retinal vessel anatomy may be useful screening tools for individuals who are at risk.

Compliance with Ethical Standards

Conflict of Interest Shaohua Guo, Songtao Yin, Gary Tse, Guangping Li, Long Su, and Tong Liu each declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
• Of importance
•• Of major importance

1.•• Nägele MP, Barthelmes J, Ludovici V, Cantatore S, Von Eckardstein A, Enseleit F, et al. Retinal microvascular dysfunction in heart failure. Eur Heart J. 2018;39(1):47–56 **One important cross-section compared the retinal vessel caliber in three groups of patients with heart failure, cardiovascular risk factors and health control.**
2.•• Seidelmann SB, Claggett B, Bravo PE, Gupta A, Farhad H, Klein BE, et al. Retinal vessel calibers in predicting long-term cardiovascular outcomes: the Atherosclerosis Risk in Communities Study. Circulation. 2016;134(18):1328–38 **The ARIC study is an ongoing, epidemiological, prospective cohort study with regard to the predictive value of retinal vessel in cardiovascular outcomes. Important results from ARIC study where relationships between retinal vessel caliber and cardiovascular results of coronary disease, heart failure, stroke and mortality are well explored.**
3. Yatsuya H, Folsom AR, Wong TY, Klein R, Klein BEK, Sharrett AR. Retinal microvascular abnormalities and risk of lacunar stroke: atherosclerosis risk in communities study. Stroke. 2010;41(7): 1349–55.
4. Wong TY, Knudtson MD, Klein R, Klein BEK, Hubbard LD. A prospective cohort study of retinal arteriolar narrowing and mortality. Am J Epidemiol. 2004;159(9):819–25.
5. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol. 2009;62(10):1006–12.
6.•• Al-Fiadh AH, Wong TY, Kawasaki R, Clark DJ, Patel SK, Freeman M, et al. Usefulness of retinal microvascular endothelial dysfunction as a predictor of coronary artery disease. Am J Cardiol. 2015;115(5):609–13 **This study put forward opposite opinion on the role of retinal vessel calibers on coronary artery disease.**
7. Cheng L, Barlis P, Colville D, Hutchinson A, Gleason G, Lamoureux E, et al. Hypertensive and diabetic microvascular retinopathy, and angiographically-demonstrated coronary artery disease: a crosssectional, observational study. Nephrology. 2016;21:63.
8. Gopinath B, Chiha J, Plant AJH, Thiagalingam A, Burlutsky G, Kovoor P, et al. Associations between retinal microvascular structure and the severity and extent of coronary artery disease. Atherosclerosis. 2014;236(1):25e30.
9. Kralev S, Zimmerer E, Buchholz P, Lin J, Economopoulou M, Lang S, et al. Microvascular retinal changes in patients presenting with acute coronary syndromes. Microvasc Res. 2010;79(2):150–3.
10. Kreis AJ, Nguyen TT, Wang JJ, Rogers S, Al-Fiadh A, Freeman M, et al. Are retinal microvascular caliber changes associated with severity of coronary artery disease in symptomatic cardiac patients? Microcirculation. 2009;16(2):177–81.
11.• McGeechan K, Liew G, Macaskill P, Irwig L, Klein R, Sharrett AR, 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 **Results form ARIC study to support the role of retinal vessel in predicting coronary artery disease.**
12. McGeechan K, Liew G, Macaskill P, Irwig L, Klein R, Klein BEK, et al. Meta-analysis: retinal vessel caliber and risk for coronary heart disease. Ann Intern Med. 2009;151(6):404–13.
13. 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.
14. Wong TY, Klein R, Sharrett AR, Duncan BB, Couper DJ, Tielsch JM, et al. Retinal arteriolar narrowing and risk of coronary heart disease in men and women: the Atherosclerosis Risk in Communities Study. J Am Med Assoc. 2002;287(9):1153–9.
15.• Wong TY, Kamineni A, Klein R, Sharrett AR, Klein BE, Siscovick DS, 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 **One of publications prospectively evaluated the role of retinal vessel calibre in predicting coronary disease.**
16.•• Chandra A, Seidelmann S, Claggett B, Klein B, Klein R, Shah A, 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;21(10):1207–15 **The most updated results from ARIC study drew opposite conclusion with previous results.**

17. Gopinath B, Wang SB, Liew G, Phan K, Joachim N, Burlutsky G, et al. Retinal vascular geometry and the prevalence of atrial fibrillation and heart failure in a clinic-based sample. Heart Lung Circ. 2018.
18. Phan K, Mitchell P, Liew G, Plant AJ, Wang SB, Au C, et al. Association between retinal arteriolar and venule calibre with prevalent heart failure: a cross-sectional study. PLoS One. 2015;10(12): e0144850.
19. Cheung CYL, Tay WT, Ikram MK, Ong YT, De Silva DA, Chow KY, et al. Retinal microvascular changes and risk of stroke: the Singapore Malay eye study. Stroke. 2013;44(9):2402–8.
20. Cooper LS, Wong TY, Klein R, Sharrett AR, Bryan RN, Hubbard LD, et al. Retinal microvascular abnormalities and MRI-defined subclinical cerebral infarction: the Atherosclerosis Risk in Communities Study. Stroke. 2006;37(1):82–6.
21. Dumitrascu OM, Demaerschalk BM, Valencia Sanchez C, Almader-Douglas D, O'Carroll CB, Aguilar MI, et al. Retinal microvascular abnormalities as surrogate markers of cerebrovascular ischemic disease: a meta-analysis. J Stroke Cerebrovasc Dis. 2018;27(7):1960–8.
22. Kawasaki R, Che Azemin MZ, Kumar DK, Tan AG, Liew G, Wong TY, et al. Fractal dimension of the retinal vasculature and risk of stroke: a nested case-control study. Neurology. 2011;76(20):1766–7.
23. Kawasaki R, Xie J, Cheung N, Lamoureux E, Klein R, Klein BEK, et al. Retinal microvascular signs and risk of stroke: the Multi-Ethnic Study of Atherosclerosis (MESA). Stroke. 2012;43(12): 3245–51.
24.• McGeechan K, Liew G, MacAskill P, Irwig L, Klein R, Klein BEK, et al. Prediction of incident stroke events based on retinal vessel caliber: a systematic review and individual-participant meta-analysis. Am J Epidemiol. 2009;170(11):1323–32 **This is a meta-analysis of studies exploring the relationship between stoke and retinal vessel caliber concluded that only wider retinal venular caliber independently increase the risk of stroke.**
25. Wieberdink RG, Ikram MK, Koudstaal PJ, Hofman A, Vingerling JR, Breteler M. Retinal vascular calibers and the risk of intracerebral hemorrhage and cerebral infarction: the Rotterdam study. Stroke. 2010;41(12):2757–61.
26. Wu HQ, Wu H, Shi LL, Yu LY, Wang LY, Chen YL, et al. The association between retinal vasculature changes and stroke: a literature review and meta-analysis. Int J Ophthalmol. 2017;10(1):109–14.
27. Arnould L, Binquet C, Guenancia C, Alassane S, Kawasaki R, Daien V, et al. Association between the retinal vascular network with Singapore "I" Vessel Assessment (SIVA) software, cardiovascular history and risk factors in the elderly: the Montrachet study, population-based study. PLoS One. 2018;13(4):e0194694.
28. Roy MS, Klein R, Janal MN. Relationship of retinal vessel caliber to cardiovascular disease and mortality in African Americans with type 1 diabetes mellitus. Arch Ophthalmol. 2012;130(5):561–7.
29. Wang JJ, Liew G, Klein R, Rochtchina E, Knudtson MD, Klein BE, et al. Retinal vessel diameter and cardiovascular mortality: pooled data analysis from two older populations. Eur Heart J. 2007;28(16): 1984–92.
30. Wong TY, Klein R, Nieto FJ, Klein BEK, Sharrett AR, Meuer SM, et al. Retinal microvascular abnormalities and 10-year cardiovascular mortality: a population-based case-control study. Ophthalmology. 2003;110(5):933–40.
31. Ikram MK, De Jong FJ, Vingerling JR, Witteman JCM, Hofman A, Breteler MMB, et al. Are retinal arteriolar or venular diameters associated with markers for cardiovascular disorders? The Rotterdam study. Investig Ophthalmol Vis Sci. 2004;45(7):2129–34.
32. Mimoun L, Massin P, Steg G. Retinal microvascularisation abnormalities and cardiovascular risk. Arch Cardiovasc Dis. 2009;102(5):449–56.
33. Leontidis G, Al-Diri B, Hunter A. Summarising the retinal vascular calibres in healthy, diabetic and diabetic retinopathy eyes. Comput Biol Med. 2016;72:65–74.
34. Wang SB, Mitchell P, Plant AJH, Phan K, Liew G, Thiagalingam A, et al. Metabolic syndrome and retinal microvascular calibre in a high cardiovascular disease risk cohort. Br J Ophthalmol. 2016;100(8):1041–6.
35. 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.
36. Marina Breysse M, Poblete Garcia VM, Lopez Mesa I, Estero Serrano De La Cruz H, Piqueras Flores J, Lopez Lluva MT, et al. RETICARD SPECT sub-study: Correlation between heart muscle perfusion and severity of hypertensive, diabetic or aterosclerotic retinopathy in patients with suspected stable coronary artery disease. Eur Heart J. 2014;35:1134.
37. Cheung N, Wang JJ, Klein R, Couper DJ, Sharrett AR, Wong TY. Diabetic retinopathy and the risk of coronary heart disease: the Atherosclerosis Risk in Communities Study. Diabetes Care. 2007;30(7):1742–6.
38. Kumar GK, Kumar A. Association between coronory artery disease and retinal artery changes. Indian Heart J. 2014;66:S39.
39. Wang SB, Mitchell P, Liew G, Wong TY, Phan K, Thiagalingam A, et al. A spectrum of retinal vasculature measures and coronary artery disease. Atherosclerosis. 2018;268:215–24.
40. Marti CN, Gheorghiade M, Kalogeropoulos AP, Georgiopoulou VV, Quyyumi AA, Butler J. Endothelial dysfunction, arterial stiffness, and heart failure. J Am Coll Cardiol. 2012;60(16):1455–69.
41. Tikellis G, Arnett DK, Skelton TN, Taylor HW, Klein R, Couper DJ, 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):352–9.
42. Cheung N, Bluemke DA, Klein R, Sharrett AR, Islam FM, Cotch MF, et al. Retinal arteriolar narrowing and left ventricular remodeling: the multi-ethnic study of atherosclerosis. J Am Coll Cardiol. 2007;50(1):48–55.
43. Barthelmes J, Montero D, Haider TJ, Naegele MP, Cantatore S, Sudano I, et al. Retinal microvascular impairment in heart failure with preserved ejection fraction. Eur Heart J. 2018;39:1385.
44. Kwa VI, van der Sande JJ, Stam J, Tijmes N, Vrooland JL. Retinal arterial changes correlate with cerebral small-vessel disease. Neurology. 2002;59(10):1536–40.
45. Wong TY. Is retinal photography useful in the measurement of stroke risk? Lancet Neurol. 2004;3(3):179–83.
46. Baker ML, Hand PJ, Wang JJ, Wong TY. Retinal signs and stroke: revisiting the link between the eye and brain. Stroke. 2008;39(4): 1371–9.
47. Yuanyuan Z, Jiaman W, Yimin Q, Haibo Y, Weiqu Y, Zhuoxin Y. Comparison of prediction models based on risk factors and retinal characteristics associated with recurrence one year after ischemic stroke. J Stroke Cerebrovasc Dis. 2020;104581.
48. Daugherty SL, Powers JD, Magid DJ, Tavel HM, Masoudi FA, Margolis KL, et al. Incidence and prognosis of resistant hypertension in hypertensive patients. Circulation. 2012;125(13):1635–42.
49. Messerli FH, Rimoldi SF, Bangalore S. The transition from hypertension to heart failure: contemporary update. JACC Heart Fail. 2017;5(8):543–51.
50. Si XB, Liu W. Relationship between blood lipid and arterial stiffness in hypertension. Clin Invest Med. 2019;42(3):E47–e55.
51. Mitchell GF. Effects of central arterial aging on the structure and function of the peripheral vasculature: implications for end-organ damage. J Appl Physiol (1985). 2008;105(5):1652–60.
52. Smith W, Malan NT, Schutte AE, Schutte R, Mc Mels C, Vilser W, et al. Retinal vessel caliber and its relationship with nocturnal blood

pressure dipping status: the SABPA study. Hypertens Res. 2016;39(10):730–6.
53. Sarwar N, Gao P, Seshasai SR, Gobin R, Kaptoge S, Di Angelantonio E, et al. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. Lancet. 2010;375(9733):2215–22.
54. Sasongko MB, Wong TY, Nguyen TT, Cheung CY, Shaw JE, Kawasaki R, et al. Retinal vessel tortuosity and its relation to traditional and novel vascular risk markers in persons with diabetes. Curr Eye Res. 2016;41(4):551–7.
55. Fontana L. Interventions to promote cardiometabolic health and slow cardiovascular ageing. Nat Rev Cardiol. 2018;15(9):566–77.
56. Neville CE, Montgomery S, Silvestri G, McGowan A, Moore E, Silvestri V, et al. Dietary patterns and retinal vessel caliber in the Irish Nun Eye Study. J Nutr Health Aging. 2018;22(7):751–8.
57. Karatzi K, Aissopou EK, Tsirimiagou C, Fatmeli E, Sfikakis PP, Protogerou AD. Association of consumption of dairy products and meat with retinal vessel calibers in subjects at increased cardiovascular risk. Nutr Metab Cardiovasc Dis. 2016;26(8):752–7.
58. Sanada F, Taniyama Y, Muratsu J, Otsu R, Shimizu H, Rakugi H, et al. Source of chronic inflammation in aging. Front Cardiovasc Med. 2018;5:12.
59. Alem MM. Endothelial dysfunction in chronic heart failure: assessment, findings, significance, and potential therapeutic targets. Int J Mol Sci. 2019:20(13).
60. Griffith TM, Edwards DH, Randall MD. Blood flow and optimal vascular topography: role of the endothelium. Basic Res Cardiol. 1991;86(Suppl 2):89–96.
61. Youngblood H, Robinson R, Sharma A, Sharma S. Proteomic biomarkers of retinal inflammation in diabetic retinopathy. Int J Mol Sci. 2019;20(19).