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ORIGINAL ARTICLE

The application of arterio-venous ratio (AVR) cut-off values in clinic to stratify cardiovascular risk in patients

Christian French[1,2] | Robert Peter Cubbidge[3] | Rebekka Heitmar[4]

[1]Department of Clinical, Biological & Pharmaceutical Science, University of Hertfordshire, Hatfield, UK

[2]Kettering General Hospital, Kettering, UK

[3]ABDO College, Godmersham Park, Canterbury, UK

[4]Centre for Vision across the LifeSpan (CVLS), School of Applied Sciences, University of Huddersfield, Huddersfield, UK

Correspondence
Christian French and Rebekka Heitmar, Department of Clinical, Biological & Pharmaceutical Science, University of Hertfordshire, Hatfield, UK.
Emails: c.french5@herts.ac.uk; r.heitmar@hud.ac.uk

Abstract

Introduction: Cardiovascular risk calculators are a useful tool for identifying at-risk individuals. There are standardised methods for assessing the retinal microcirculation which alters as a consequence of cardiovascular disease (CVD). This study aimed to explore if a standardised retinal vessel assessment conducted in primary optometric care reflects current cardiovascular risk, as measured using two validated CVD risk calculators (QRISK 2; Mayo Clinic).

Methods: A total of 120 subjects were included in the analyses. Following a routine eye examination, participants had disc-centred retinal photographs and systemic blood pressure taken. Retinal vessel parameters (central retinal artery and vein equivalent and arterio-venous ratio (AVR)) were calculated using semi-automated software. Participants were then grouped into AVR quintiles as defined by the Atherosclerosis Risk in Communities Study (ARIC). Cardiovascular risk was calculated with the validated QRISK and Mayo Clinic health calculators.

Results: Systolic blood pressure was significantly greater in those with an AVR value falling in the lowest quintile compared to the highest quintile (150.65 mmHg vs. 132.21 mmHg [$p = 0.001$]). Similarly, CVD risk was significantly higher in those with the lowest AVR compared to the highest (QRISK: 14.28% vs. 9.87% [$p = 0.05$]; MAYO risk: 36.35% vs. 19.21% [$p = 0.01$]). Chi squared analyses showed a significant difference in the number of hypertensives in the lowest AVR quintile compared to those in the highest [$p = 0.02$].

Conclusion: Whilst the ARIC population is not directly comparable to the population used to develop the QRISK calculator, it has been shown that its application could help to identify at risk individuals using retinal vessel analyses.

KEYWORDS
AV ratio, cardiovascular disease, optometry, retinal blood vessel

INTRODUCTION

It is not yet possible to say with absolute certainty when individuals will develop cardiovascular disease (CVD). Therefore, healthcare must rely on probability-based models to estimate risk. Metrics correlating with incident CVD are recorded and input into an algorithm to produce an estimate of risk within a pre-defined timeframe.[1,2] Through application of such calculators and stratifying individuals by risk, intervention and management strategies can be

prioritised for those in greatest need.[3] Those with pre-existing cardiovascular pathology are known to be at increased risk of developing co-morbidities, but of equal concern are those who are generally asymptomatic, where it is known that a number of modifiable risk factors (such as cholesterol levels, smoking, exercise and blood pressure) play a significant role.

Prevention being better than cure, health guidelines advocate the use of such calculators to aid the identification of 'at risk' individuals.[3] A significant contributor to algorithm development has been the Framingham Study, based in the USA. Having begun data collection in 1948 and run continually thereafter (the grandchild cohort was enrolled in 2002), the study has yielded vital long-term health data.[4,5] The validity of such calculators when applied to other cohorts (i.e., internationally) has been highlighted, and in the UK has led to the development of an alternative algorithm derived from local data: QRISK, which calculates 10-year risk of an incident CVD event.[2,6] This calculator has undergone two subsequent revisions (in order to incorporate more variables) in 2008 and 2017: QRISK2 and QRISK3, respectively.[7,8] When validated against a Framingham-derived calculator, QRISK demonstrated better discrimination between high and low-risk individuals.[7] The calculators are freely available to access online, and the National Institute for Health and Care Excellence (NICE) advocate their use in routine screening of potential 'at risk' patients; currently, intervention is advised for risk scores of 10% or greater. In an effort to identify asymptomatic, at risk individuals, the National Health Service (NHS) operates a 5-yearly, invitation-based Health Check for those aged between 40 and 74. Although this service is free of charge and includes a range of tests (including blood pressure, lifestyle assessment and blood tests), average annual attendance is presently only around 44.7%, suggesting a significant proportion of the UK population may still be unknowingly at risk of a CVD event.[9]

Concurrently, significant progress has been made in the measurement and understanding of the retinal microcirculation. Until recently, quantification of changes to the retinal microcirculation were rooted in the early observations of Gowers and Gunn at the end of the 19th century, and the work of Keith, Wagener and Barker (KWB) in the 1930s.[10–12] The KWB classification was the first major attempt to correlate the visible appearance of the retina and the mortality of patients, and is still occasionally used in research (although its use is waning).[13,14] Additionally, UK optometrists are still expected to record the retinal vasculature subjectively by The College of Optometrists.[15] Whilst it is widely acknowledged that retinal vessel health correlates with cardiovascular status, no management criteria or referral pathway currently exists based on retinal findings, nor is blood pressure routinely measured. Current best practice guidelines advocate the use of the subjective arterio-venous ratio (AVR) and descriptive observations of the retinal vasculature, despite historical observations of limitations to such subjective approaches.[16,17]

> **Key points**
> - Retinal vessel calibre assessments in primary eye care can be useful biomarkers to complement cardiovascular risk stratification.
> - Retinal vascular calibres may be useful as a surrogate marker of cardiovascular health.
> - Data obtained during primary eye care examinations could be used for the clinical benefit of otherwise healthy individuals to examine their cardiovascular risk.

Technological advancements, chiefly the advent of digital retinal imaging, now allow for objective techniques to assess and quantify a range of characteristics of the retinal microvasculature; for example, vessel calibre,[18,19] tortuosity,[20–22] branching angle and fractal dimensions[23,24] and oxygen saturation.[25] Of these parameters, retinal vessel calibre has a wealth of data correlating it with other measures of cardiovascular health. Whilst a number of these concern arterial or venular calibre changes independent of one another, depending on underlying pathologies (such as the central retinal artery equivalent (CRAE) decrease in raised blood pressure[18,26–28] and the central retinal vein equivalent (CRVE) increases in complications associated with diabetes mellitus[29–32] and stroke[33–35]), there is also evidence which suggests that an objectively derived AVR correlates well with cardiovascular health.[18,33,36–42]

Considering the significant shortfall in attendance at the NHS Health Checks, additional routes of access to screening are necessary to improve identification of those at risk. The age-range targeted (40–74 years) roughly corresponds to the onset of symptomatic presbyopia. Additionally, the optometrist's consulting room has been demonstrated to be an effective location for measuring blood pressure.[43] Considering this, in conjunction with the regularity of eye examinations (typically every 1–2 years), the recording of medical history and lifestyle, as well as the examination of the retinal microvasculature, an optometrist's consulting room has the potential to be a vital additional source of routine cardiovascular screening with little additional work.

For optometrists to contribute effectively to routine cardiovascular health screening, management pathways and clinical decision-making matrices need to be developed in line with established routes. A distinct intervention point has been defined in the UK with QRISK scores (i.e., ≥10%); the same needs to be the case with retinal vessel assessments which should follow a standardised protocol. The Atherosclerosis Risk in Communities (ARIC) Study (which outlined the use of retinal vessel calibre measurement) reported that AVRs in the lowest quintile were 24-times more likely to develop incident stroke over a 3.5 year period compared to the uppermost quintile,[44] suggestive of
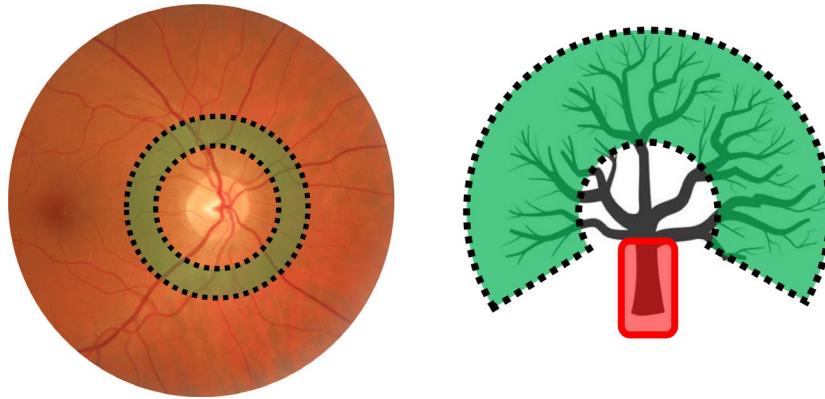
FIGURE 1 [Left] Measurement zone on retinal photographs for recording retinal vessel calibre (between ½ and 1 full disc diameter from the optic nerve head). [Right] The process works much like measuring the width of the branches of a tree to estimate the width of the trunk from which they originate. In the case of retinal vessel analysis, the trunk (i.e. the central retinal artery or vein) is not directly visible; hence the measurement is referred to as a central retinal artery/vein equivalent

a poor cardiovascular health profile. In the absence of specific intervention criteria, comparing AVR measurements to these quintile measurements and their correlation with QRISK predictions may identify patients who benefit most from further health assessments.

METHODS

The study was approved by the Aston University Research Ethics Committee (Reference 778) and adhered to the tenets of the Declaration of Helsinki. Participants were patients attending for a routine eye examination at a UK optometry practice (Davis Optometrists, Market Harborough, UK), and gave written informed consent prior to their examination.

Inclusion criteria for the study were as follows: aged between 51–70 years (in order to match the original ARIC cohort, since vessel calibre has been shown to vary with age) and a good quality fundus photograph of at least one eye. Patients with dense cataracts, corneal scarring or other media opacity which negatively affected image quality were excluded.

Ocular examination

All participants underwent a full eye examination, including subjective sphero-cylindrical refraction, ophthalmoscopic examination (using slit lamp biomicroscopy and a 78D condensing lens) and combined fundus photography and optical coherence tomography (OCT; Topcon 3D Maestro (Topcon, global.topcon.com)). Undilated (unless otherwise indicated) full-colour, 45° optic nerve head-centred photographs were acquired with the Topcon 3D Maestro and stored in the highest resolution format available, Tagged Image File Format (TIFF). Following image acquisition, all images were assigned a unique identification number and a quality index as detailed elsewhere.[45] In brief, images

were rated on a scale of 1–5, whereby a minimum quality of 4 was set as the cut-off value to be included for further analyses.

Systemic blood pressure (BP) was obtained using a digital sphygmomanometer (UA-767, A&D Medical, medical.andprecision.com) per National Institute for Health and Care Excellence (NICE) and European Societies of Hypertension (ESH) and Cardiology (ESC) guidelines;[46,47] the patient was seated for at least 5 min and three readings were taken with 1-min intervals. Average BP readings for systolic and diastolic blood pressure were calculated using three readings unless there was a ≥10 mmHg discrepancy.

Cardiovascular risk calculation

Detailed medical symptoms and history was recorded by the criteria required for the calculation of cardiovascular risk (Mayo Clinic[1] and QRISK2[48]). The two calculators were chosen in order to explore cardiovascular risk across different timeframes. The QRISK2 estimates 10-year risk as a percentage, whilst the Mayo Clinic predicts over a 30-year period. Whilst a newer iteration of the QRISK algorithm exists (QRISK3[49]), it has not yet been incorporated into NICE guidelines, and so was not used for the present study for that reason. Data regarding participants' general health and medical history (including medication), lifestyle (including smoking status, alcohol and caffeine intake, exercise and diet) and family medical history were all recorded according to standard clinical management guidance.[15] Height and weight were self-reported from patients. Location data (as required by QRISK2) was obtained from the participant's home address registered with the practice.

Retinal vessel calibre measurement

After the quality assessment, red-free images were imported into VesselMap v3.0 (Imedos, imedos.com) for vessel

calibre analysis. In brief, the analysis procedure is semi-automated whereby a circle corresponding to the ARIC-defined disc diameter (1850μm) is placed around the optic disc beyond which a measurement annulus (½ to 1 disc diameter; see Figure 1) is fitted. The software utilises the original Parr-Hubbard formulae,[18] where only vessels larger than 40μm are selected. Once all vessels crossing through the measurement annulus are selected, the software produces a single summary value which is an estimate of the calibre of the central retinal artery from which all of those measured arterial vessels have originated from (the central retinal artery equivalent, CRAE). This is also summarised in Figure 1. Similarly, a value is also calculated for the central retinal vein equivalent (CRVE). With a single measurement for both artery and vein, it is then possible to calculate a ratio of the two to give an objective arterio-venous ratio (AVR), where AVE =CRAE / CRVE.

All tests and image analyses were conducted by a single optometrist (CF). All images were assigned a unique identification number immediately after data collection to minimise observer bias.

Application of arterio-venous ratio (AVR) classification

The original ARIC Study report on AVR correlations with incident stroke was used as the basis for classification values.[44] This study found individuals with an AVR in the lowest quintile were 24-times more likely to develop incident stroke within 3.5 years compared to those with an AVR in the uppermost quintile. This was used as a benchmark for signifying impaired cardiovascular health, and used in the present study. While they refer to AVR quintiles, specific numerical values for these were not published. Hence, these were kindly provided by the paper's original statistician (David Couper, personal communication, 2 July 2019; see Table 1). Since these quintile values relate specifically to the ARIC dataset, the uppermost and lowest values will be referred to as 'cut off' values in this paper.

Statistical analysis

All data were analysed using SPSS v26.0 (IBM, ibm.com). Normal distribution was evaluated by Kolmogorov-Smirnov testing for each variable. Following a paired samples t-test comparing right and left eye vessel parameters, average inter-eye (OU) parameters were calculated from vessel calibre measurements and used for subsequent analyses (CRAE $t = -0.10$, $p = 0.92$; CRVE $t = -0.25$, $p = 0.80$; AVR $t = 0.15$; $p = 0.78$). In order to assess if AVR values reflect current cardiovascular risk as calculated by QRISK2 and Mayo Clinic, participants falling outside the uppermost and lowest ARIC quintile measurements were compared. In addition, Chi squared tests were employed on categorical

data to compare the prevalence in each group (as defined by the upper and lower ARIC quintiles). Statistical significance was defined as $p \leq 0.05$.

TABLE 1 Absolute quintile values as derived from the Atherosclerosis Risk in the Communities Study (ARIC) when correlating with incident stroke as reported by Wong et al[44]

Quintile	AVR range
Fifth	>0.90642
Fourth	0.86090–0.90642
Third	0.82157–0.86090
Second	0.77746–0.82157
First	<0.77746

Note: Values were obtained via personal communication with the lead statistician (David Couper, 2 July 2019).

Abbreviation: AVR, application of arterio-venous ratio.

RESULTS

One hundred and twenty-five patients met the inclusion criteria, but five were excluded due to insufficient image quality (being Grade 2 or less[45]), leaving a total of 120 to be included for statistical analysis. Table 2 details subjects' demographics, ocular and cardiovascular risk data. In total, 72 were female and mean age was 59.59 years (±6.04). Mean CRAE for the right and left eyes was 170.75 μm (±16.30) and 170.95 μm (±16.13), respectively, while the inter-eye average (OU) CRAE was 170.60 μm (±15.30). Mean CRVE for right and left eyes was 201.73 μm (±17.54) and 202.09 μm (±16.69) respectively, whilst OU average CRVE was 201.29 μm (±16.48). A mean AVR of 0.85 (±0.07) was recorded in both eyes, also giving an OU average of 0.85 (±0.07). Both normal quantile-quantile plots and Kolmogorov-Smirnov revealed data for all variables to be normally distributed. Distribution of inter-eye average AVRs plotted against age is shown in Figure 2, with the ARIC quintiles overlayed for reference.

Following AVR stratification (as detailed in Table 1), a total of 19 subjects had an AVR greater than the upper cut-off (0.90642), whilst 17 had an AVR less than the lower AVR quintile cut-off (0.77746). Independent t-tests were run between these two samples; Levene's Test for Equality of Variance was significant for all parameters.

Both systolic blood pressure (SBP) and diastolic blood pressure (DBP) were found to be significantly higher amongst those subjects falling below the lower AVR cut-off compared to those with an AVR greater than the higher cut off (SBP: 150.65 vs. 132.21 mmHg; DBP: 91.65 vs. 82.47 mmHg (both $p = 0.001$)). Mean CRAE was found to be significantly reduced (−26.04 μm) amongst individuals falling below the lower AVR cut-off ($p = <0.001$) whilst mean CRVE was found to be increased by 19.59μm amongst the same subjects ($p = 0.002$).

Cardiovascular risk, as calculated by QRISK2 and the Mayo Clinic, was significantly greater for subjects with an AVR

TABLE 2 Summary of cohort demographics, tabulated for the whole cohort with standard deviations shown in parentheses

Variable	Whole cohort	Lower AVR cut-off (<0.77746)	Upper AVR cut-off (>0.90642)	Significance
n	120	17	19	*p*
Gender: Female [Male]	72 [48]	10 [7]	12 [7]	0.80
	Mean (SD)	Mean (SD)	Mean (SD)	
Age (years)	60 (6)	61 (6)	61 (6)	0.71
SBP (mmHg)	134 (19)	151 (14)	132 (16)	**0.001**
DBP (mmHg)	85 (11)	92 (2)	82 (11)	**0.01**
Height (m)	1.72 (± 0.05)	1.73 (± 0.06)	1.72 (± 0.04)	0.43
Weight (kg)	77 (10)	79 (12)	73 (11)	0.11
BMI (kg/m^2)	26 (3)	27 (4)	25 (3)	0.12
CRAE (μm)	171 (15)	153 (13)	179 (18)	**<0.001**
CRVE (μm)	201 (16)	208 (18)	188 (17)	**0.002**
AVR	0.85 (±0.07)	0.73 (±0.02)	0.95 (±0.03)	**<0.001**
QRISK 10-year risk (%)	10.77 (±7.18)	14.28 (±7.34)	9.87 (±4.89)	**0.05**
Mayo Clinic 30-year risk (%)	28.36 (±19.04)	36.35 (±21.17)	19.21 (±16.67)	**0.01**

Note: Mean data is then shown for subjects with an AVR above or below the uppermost and lowest ARIC quintiles, respectively. Independent *t*-tests were run on these two groups, and significance is shown in the rightmost column (significant values shown in bold).

Abbreviations: ARIC, Atherosclerosis Risk in the Communities Study; AVR, arterio-venous ratio; BMI, body mass index; CRAE, central retinal artery equivalent; CRVE, central retinal vein equivalent; DBP, diastolic blood pressure; SBP, systolic blood pressure; Vessel summary measurements (CRAE, CRVE and AVR) are all inter-eye averages (OU).

less than the lower cut-off when compared to those with an AVR greater than the upper cut-off. Mean QRISK2 was 4.41% greater (14.28% vs. 9.87%; *p* = 0.05) whilst the Mayo Clinic calculation was 17.14% greater (36.35% vs. 19.21%; *p* = 0.01) compared to those with an AVR greater than the upper cut-off. Chi squared showed a significant presence of diagnosed hypertensives in the category below the lower ARIC cut-off compared to the upper cut-off. There was no significant difference in BMI nor its components (i.e., height and weight) between the two groups (*p* ≥ 0.05).

The distribution of pathologies and variables associated with cardiovascular disease is explored in greater detail in Table 3. Chi squared tests revealed that there was a significant difference in the number of subjects with diagnosed hypertension with an AVR below the lowest ARIC quintile (*p* = 0.02). Additionally, there was a significant difference in the number of persons taking calcium channel blockers (*p* = 0.05). All other distributions were not statistically different.

DISCUSSION

This study evaluated whether AVR cut-off values, as defined by the ARIC Study, are linked with markers of cardiovascular risk when assessed in a primary care optometric setting. The basis of this work was to take the findings of the original ARIC Study, which has well-documented strong correlations between AVR and cardiovascular outcomes, and uses them as a benchmark. The authors of the ARIC Study found that individuals with an AVR in the lowest quintile were 24-times more likely to develop incident stroke within 3.5 years compared to those with an AVR in the uppermost quintile. For the present study, this finding was deemed to be highly suggestive of poor cardiovascular health, and used to compare with established systemic predictors of cardiovascular health (i.e., risk calculators). Our results demonstrate that individuals in the lowest AVR quintile presented with an increased level of CVD risk markers compared to those in the highest AVR quintile.

Using the absolute values determined by the original ARIC investigators, the AVR measurements of the present cohort were stratified to identify those with AVRs in-line with the original study. Comparing these two groups, it has been shown that there is a clear difference in vessel calibre, with arterial narrowing and venular dilation being observed in the lower cut-off group. Both of these vessel changes have been linked elsewhere to cardiovascular disease (reduced arterial calibre is strongly associated with raised blood pressure,[26,36,50,51] and venular dilation has been associated with both the onset of diabetes mellitus[38,52] and stroke[33,35,42,53]). In addition, cardiovascular risk was found to be greater in the lower cut-off group. The QRISK2 algorithm has been generated from UK-based data, which is arguably a better representation of cardiovascular risk amongst the present cohort compared to the Mayo Clinic algorithm; the latter being derived from Framingham Risk Study data in the USA. The QRISK2 algorithm estimates risk over a 10-year period, whereas the Mayo Clinic is designed to show risk over a more extended period (30 years). That both calculations are significantly greater in the lower cut-off group suggests a general increase in cardiovascular risk for these individuals both in the medium and long-term.
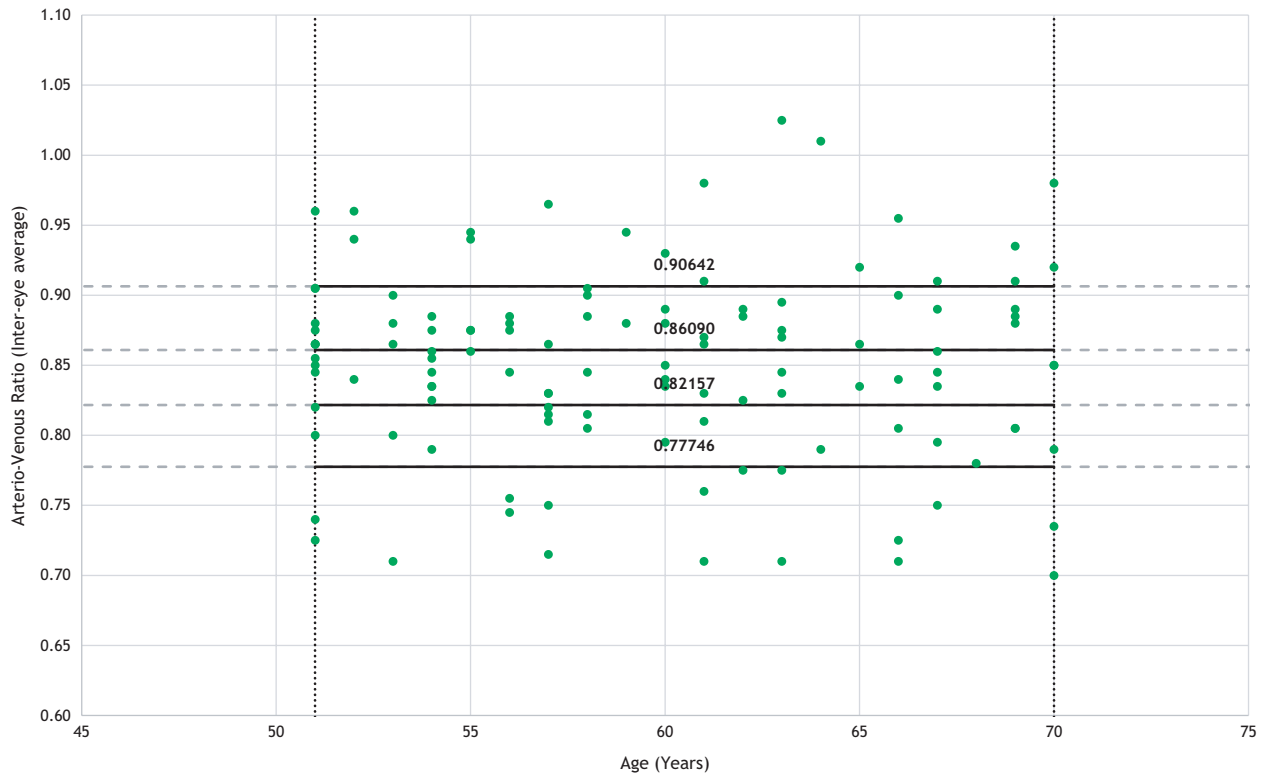
FIGURE 2 Distribution of inter-eye average AVR against age. The ARIC age-range (51–70 years) and quintiles are overlayed for reference. ARIC, Atherosclerosis Risk in Communities Study; AVR, arterio-venous ratio

TABLE 3 Chi-squared tests for association between subjects falling beyond the ARIC AVR quintile cut-offs

Variable	Whole cohort	Lower AVR cut-off (<0.77746)	Upper AVR cut-off (>0.90642)	Chi-squared (Lower vs. Upper)
n	120	17	19	
Smoker	24	3	4	0.80
Hypertension	33	10	4	**0.02**
Diabetes mellitus:				
(Type I)	6	1	0	0.22
(Type II)	4	1	0	0.22
Heart disease	9	1	2	0.61
Co-morbid	14	0	0	
Medications:				
Calcium channel blocker	12	5	1	**0.05**
Beta-blocker	7	0	1	0.25
Angiotensin receptor blocker	2	2	0	0.08
ACE inhibitor	1	0	0	
Thiazide-like diuretic	1	0	0	

Note: Prevalence of diagnosed cardiovascular disease and co-morbidity is shown for the whole cohort and those with an AVR above or below the uppermost and lowest AVR cut-offs. Associations for prescribed medications are also shown. Significance was set at *p* ≤ 0.05 (significant values shown in bold).

Abbreviations: ARIC, Atherosclerosis Risk in the Communities Study; AVR, arterio-venous ratio.

Interestingly, a high number of previously diagnosed hypertensives were recorded in the lower cut-off group as having raised systemic blood pressure. This suggests that greater refinement and management of those cases may be warranted, since despite a confirmed diagnosis and treatment, their current BP is not well controlled.

Correlating objective retinal vessel measurements with established measures such as QRISK2 is a strong argument

for integrating this biomarker into future clinical management and referral guidelines. At present, optometrists are expected to inspect the retinal vasculature visually, and are acutely aware of characteristic changes associated with certain cardiovascular pathologies (such as hypertension). However, there is a lack of guidance on what to do with identified retinal vascular changes, and the present evaluation consists of subjective grading via ophthalmoscopy (or fundus photography). This approach has been shown to be highly inaccurate.[16] Whilst fundus photography is commonplace in primary care optometry, there is an absence of clinical management guidelines for the images. At present, the photographs are merely used for documentation instead of adding further diagnostic information. On the other hand, there is a clear pathway for the management of patients with a QRISK2 value greater than 10%;[3] the establishment of optometric management guidelines in line with this criterion would contribute to greater cohesion between healthcare disciplines. This study demonstrates that this method of objective retinal vessel assessment has good agreement with established and accepted measures of cardiovascular health.

An additional benefit of this approach is the regularity of eye examinations. The College of Optometrists recommends a maximum interval of two years, meaning frequent interactions with a primary care professional.[54] In addition, the onset of symptomatic presbyopia coincides well with the age range of the NHS Health Check scheme (i.e., >40 years old). Given the poor take up of the latter, exploration of alternative schemes for identifying at-risk persons is crucial.

Optometrists are well-placed for contributing to the detection of cardiovascular risk patients. Minimal additional information need be recorded since a thorough health and lifestyle questionnaire has already been undertaken as a matter of course during history and symptom taking. Clinical measurement of blood pressure takes a small amount of time, and the patient is already set up for the measurement, having been in the consulting room chair seated and relaxed for more than 5 min. Additionally, the vessel measurements can be performed in a matter of seconds, meaning that little additional time is required for each consultation yet yields significantly greater clinical information. Added to the two-yearly examinations, a detailed clinical profile will be quickly accumulated by the optometrist.

There are several limitations which need to be addressed in this research. The data was collected in arguably 'sub-optimal' conditions, with patients undilated (although this is representative of current routine optometric practice in the UK). Much of the medical history was self-reported; thus the specificity of recall was dependent upon the individual patient. A battery of blood tests would have better bridged the gap between structural measurement (i.e., retinal vessel calibre) and predicted cardiovascular risk. Additionally, the ARIC quintile values themselves, much like the Mayo Clinic/Framingham data, are derived from a less recent United States cohort. There has already

been some disparity shown between Framingham and European data, suggesting the date and location of the cohorts may play a role.[55] This may also be the case for the absolute AVR cut-off values derived by the ARIC study (see also Table 1), as these may well differ depending on the population assessed.

In summary, this research uniquely demonstrates that agreement exists in the principle of stratifying objective retinal vessel measurements by pre-defined cut-off values and correlating them with established metrics of cardiovascular health. It has also been shown that optometrists are well suited to perform regular non-invasive assessments of patients to identify those at risk of cardiovascular disease and provide continuous observation and co-management with other healthcare professionals, strengthening the concept of patient-centred care.

CONFLICTS OF INTEREST
The authors report no conflicts of interest and have no proprietary interest in any of the materials mentioned in this article.

AUTHOR CONTRIBUTION
Christian French: Data curation (equal); Formal analysis (equal); Funding acquisition (equal); Investigation (equal); Methodology (equal); Project administration (equal); Writing – original draft (equal); Writing – review & editing (equal). **Robert Cubbidge:** Methodology (equal); Supervision (equal); Writing – review & editing (equal). **Rebekka Heitmar:** Conceptualization (equal); Data curation (equal); Formal analysis (equal); Funding acquisition (equal); Methodology (equal); Project administration (equal); Supervision (equal); Writing – original draft (equal); Writing – review & editing (equal).

ORCID
Rebekka Heitmar https://orcid.org/0000-0002-7657-1788

REFERENCES
1. Mayo Health Clinic Systems. Heart disease risk calculator. Available from: https://www.mayoclinichealthsystem.org/locations/cannon-falls/services-and-treatments/cardiology/heart-disease-risk-calculator. Accessed 17 Jul 2021.
2. Hippisley-Cox J, Coupland C, Vinogradova Y, et al. Derivation and validation of QRISK, a new cardiovascular disease risk score for the United Kingdom: Prospective open cohort study. *Br Med J* 2007;335:136–41.
3. National Institute for Health and Care Excellence. Cardiovascular disease: risk assessment and reduction, including lipid modification [clinical guideline]. The UK National Institute for Health and Care

Excellence. 2014. Available from: www.nice.org.uk/guidance/cg181. Accessed 28 February, 2022.

4. Dawber TR, Meadors GF, Moore FE. Epidemiological approaches to heart disease: the Framingham study. *Am J Public Health* 1951;41:279–81.

5. Tsao CW, Vasan RS. Cohort profile: the Framingham heart study (FHS): overview of milestones in cardiovascular epidemiology. *Int J Epidemiol* 2015;44:1800–13.

6. Beswick A, Brindle P, Fahey T, Ebrahim S. A systematic review of risk scoring methods and clinical decision aids used in the primary prevention of coronary heart disease. *R Coll Gen Pract* 2008;4:1–361.

7. Hippisley-Cox J, Coupland C, Vinogradova Y, et al. Predicting cardiovascular risk in England and Wales: prospective derivation and validation of QRISK2. *Br Med J* 2008;336:1–15. https://doi.org/10.1136/bmj.39609.449676.25

8. Hippisley-Cox J, Coupland C, Brindle P. Development and validation of QRISK3 risk prediction algorithms to estimate future risk of cardiovascular disease: prospective cohort study. *Br Med J* 2017;357:1–21. https://doi.org/10.1136/bmj.j2099

9. National Health Service. NHS Health Check programme statistics: 2012/13-2017/18. 2019. Available from: www.gov.uk/government/statistics/nhs-health-check-programme-2012-13-to-2017-18. Accessed 28 February, 2022.

10. Gowers WR. The state of the arteries in Bright's disease. *Br Med J* 1876;2:743–5.

11. Gunn MR. On ophthalmoscopic evidence of general arterial disease. *Trans Ophthalmol Soc U K* 1898;18:356–81.

12. Keith NM, Wagener HP, Barker NW. Some different types of essential hypertension: their course and prognosis. *Am J Med Sci* 1939;197:332–43.

13. Ahn SJ, Woo SJ, Park KH. Retinal and choroidal changes with severe hypertension and their association with visual outcome. *Invest Ophthalmol Vis Sci* 2014;55:7775–85.

14. Mulè G, Nardi S, Cottone S, et al. Influence of metabolic syndrome on hypertension-related target organ damage. *J Intern Med* 2005;257:503–13.

15. The College of Optometrists What to record - clinical guidance (patient records). Available from: https://guidance.college-optometrists.org/guidance-contents/knowledge-skills-and-performance-domain/patient-records/#open:322. Accessed 17 Jul 2021.

16. Stokoe NL, Turner RWD. Normal retinal vascular pattern. *Br J Ophthalmol* 1966;50:21–41.

17. Heitmar R, Kalitzeos AA, Patel SR, Prabhu-Das D, Cubbidge RP. Comparison of subjective and objective methods to determine the retinal arterio-venous ratio using fundus photography. *J Optom* 2015;8:252–7. https://doi.org/10.1016/j.optom.2014.07.002

18. Hubbard LD, Brothers RJ, King WN, et al. Methods for evaluation of retinal microvascular abnormalities associated with hypertension/sclerosis in the Atherosclerosis Risk in Communities Study. *Ophthalmology* 1999;106:2269–80.

19. Knudtson MD, Lee KE, Hubbard LD, et al. Revised formulas for summarizing retinal vessel diameters. *Curr Eye Res* 2003;27:143–9.

20. Hart WE, Goldbaum M, Côté B, Kube P, Nelson MR. Measurement and classification of retinal vascular tortuosity. *Int J Med Inform* 1999;53:239–52.

21. Cheung CY-L, Zheng Y, Hsu W, et al. Retinal vascular tortuosity, blood pressure, and cardiovascular risk factors. *Ophthalmology* 2011;118:812–8.

22. Kalitzeos AA, Lip GYH, Heitmar R. Retinal vessel tortuosity measures and their applications. *Exp Eye Res* 2013;106:40–6.

23. Zhu P, Huang F, Lin F, et al. The relationship of retinal vessel diameters and fractal dimensions with blood pressure and cardiovascular risk factors. *PLoS One* 2014;9:1–10. https://doi.org/10.1371/journal.pone.0106551

24. Cheung CY, Thomas GN, Tay W, et al. Retinal vascular fractal dimension and its relationship with cardiovascular and ocular risk factors. *Am J Ophthalmol* 2012;154:663–74.e1.

25. Stefánsson E, Olafsdottir OB, Eliasdottir TS, et al. Retinal oximetry: Metabolic imaging for diseases of the retina and brain. *Prog Retin Eye Res* 2019;70:1–22.

26. Wong TY, Shankar A, Klein R, Klein BEK, Hubbard LD. Prospective cohort study of retinal vessel diameters and risk of hypertension. *Br Med J* 2004;329:1–5. https://doi.org/10.1136/bmj.38124.682523.55

27. Wong TY, Islam FMA, Klein R, et al. Retinal vascular caliber, cardiovascular risk factors, and inflammation: the multi-ethnic study of atherosclerosis (MESA). *Invest Ophthalmol Vis Sci* 2006;47:2341–50.

28. Tanabe Y, Kawasaki R, Wang JJ, et al. Retinal arteriolar narrowing predicts 5-year risk of hypertension in Japanese people: the Funagata study. *Microcirculation* 2010;17:94–102.

29. Klein R, Klein BEK, Moss SE, et al. The relation of retinal vessel caliber to the incidence and progression of diabetic retinopathy: XIX: the Wisconsin Epidemiologic Study of Diabetic Retinopathy. *Arch Ophthalmol* 2004;122:76–83.

30. Klein R, Klein BEK, Moss SE, et al. Retinal vascular abnormalities in persons with type 1 diabetes: the Wisconsin epidemiologic study of diabetic retinopathy: XVIII. *Ophthalmology* 2003;110:2118–25.

31. Nguyen TT, Wang JJ, Sharrett AR, et al. Relationship of retinal vascular caliber with diabetes and retinopathy - the multi-ethnic study of atherosclerosis (MESA). *Diabetes Care* 2008;31:544–9.

32. Jeganathan VSE, Sabanayagam C, Tai ES, et al. Retinal vascular caliber and diabetes in a multiethnic Asian population. *Microcirculation* 2009;16:534–43.

33. 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;166:2388–94.

34. Wieberdink RG, Ikram MK, Koudstaal PJ, et al. Retinal vascular calibers and the risk of intracerebral hemorrhage and cerebral infarction: the Rotterdam study. *Stroke* 2010;41:2757–61.

35. Fani L, Bos D, Mutlu U, et al. Global brain perfusion and the risk of transient ischemic attack and ischemic stroke: the Rotterdam study. *J Am Heart Assoc* 2019;8:e011565. https://doi.org/10.1161/JAHA.118.011565

36. Ikram MK, Witteman JCM, Vingerling JR, et al. Retinal vessel diameters and risk of hypertension – the Rotterdam study. *Hypertension* 2006;47:189–94.

37. Wong TY, Shankar A, Klein R, Klein BEK, Hubbard LD. Retinal arteriolar narrowing, hypertension, and subsequent risk of diabetes mellitus. *Arch Intern Med* 2005;165:1060–5.

38. Ikram MK, Janssen JAMJL, Roos AME, et al. Retinal vessel diameters and risk of impaired fasting glucose or diabetes: the Rotterdam study. *Diabetes* 2006;55:506–10.

39. Cheung N, Rogers SL, Donaghue KC, et al. Retinal arteriolar dilation predicts retinopathy in adolescents with type 1 diabetes. *Diabetes Care* 2008;31:1842–6.

40. Cooper LS, Wong TY, Klein R, et al. Retinal microvascular abnormalities and mri-defined subclinical cerebral infarction: the atherosclerosis risk in communities study. *Stroke* 2005;37:82–6.

41. Wong TY, Klein R, Nieto FJ, et al. Retinal microvascular abnormalities and 10-year cardiovascular mortality. *Ophthalmology* 2003;110:933–40.

42. Ikram MK, de Jong FJ, Bos MJ, et al. Retinal vessel diameters and risk of stroke – the Rotterdam study. *Neurology* 2006;66:1339–43.

43. Alanazi SA, Osuagwu UL, Almubrad TM, Ahmed HK, Ogbuehi KC. Effectiveness of in-office blood pressure measurement by eye care practitioners in early detection and management of hypertension. *Int J Ophthalmol* 2015;8:612–21.

44. Wong TY, Klein R, Couper DJ, et al. Retinal microvascular abnormalities and incident stroke: the atherosclerosis risk in communities study. *Lancet* 2001;358:1134–40.

45. Lamirel C, Bruce BB, Wright DW, et al. Quality of nonmydriatic digital fundus photography obtained by nurse practitioners in the emergency department: the FOTO-ED study. *Ophthalmology* 2012;119:617–24.

46. National Institute for Health and Care Excellence. Hypertension in adults: diagnosis and management [clinical guideline]. 2011.

Available from: https://www.nice.org.uk/guidance/ng136. Accessed 28 February, 2022.

47. Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: the task force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J* 2013;34:2159–219.

48. ClinRisk Ltd. QRISK2. Available from: https://qrisk.org/2017/ Published 2017. Accessed 18 Jul 2021.

49. ClinRisk Ltd. QRISK3. Available from: https://qrisk.org/three/ Published 2018. Accessed 18 Jul 2021.

50. 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;44:4644–50.

51. Smith W, Wang JJ, Wong TY, et al. Retinal arteriolar narrowing is associated with 5-year incident severe hypertension: the blue mountains eye study. *Hypertension* 2004;44:442–7.

52. 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;15:373–7.

53. Lindley RI, Wang JJ, Wong MC, et al. Retinal microvasculature in acute lacunar stroke: a cross-sectional study. *Lancet Neurol* 2009;8:628–34.

54. Wright DM, O'Reilly D, Azuara-Blanco A, et al. Delayed attendance at routine eye examinations is associated with increased probability of general practitioner referral: a record linkage study in Northern Ireland. *Ophthalmic Physiol Opt* 2020;40:365–75.

55. Hippisley-Cox J, Coupland C, Vinogradova Y, Robson J, Brindle P. Performance of the QRISK cardiovascular risk prediction algorithm in an independent UK sample of patients from general practice: A validation study. *Heart* 2008;94:34–9.

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