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The Eyes as a Window to the Heart: Looking Beyond the Horizon

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Despite significant advances in prevention and treatment, cardiovascular disease (CVD) remains a significant cause of mortality and morbidity. CVD is the most common cause of death worldwide, and its burden is increasing.[2] In the United Kingdom it accounts for a quarter of all deaths.[1] Given the morbidity associated with CVD, identification of individuals at high risk is particularly important.

Currently clinical risk scores such as the QRISK assessment tool[3] are recommended for evaluating CVD risk.[4, 5] Tools such as these use a combination of clinical variables, risk factors and laboratory tests to calculate an individual's CVD risk over a period of time (typically 10 years). If the calculated level of risk is above a set threshold then preventative therapy such as statins are recommended. These risk scores are widely validated and tend to perform well, with a Harrel's C-statistic of ~0.8, although the C-statistic is sometimes lower in studies using other populations to those from which the scores were derived.[6] It is accepted that these tools are unfortunately not perfect, and there will be individuals who are assigned a low or intermediate clinical risk and therefore not started on preventative therapy who still have CVD.[7]

The retina is the only location that allows non-invasive direct visualisation of the vasculature, potentially providing a rich source of information. The retina is sensitive to changes in CVD risk factors such as glycaemia and blood pressure, which of course provides the rationale for routine diabetic retinopathy screening. The association between retinal features and CVD has been well-studied, with the presence of diabetic or hypertensive retinopathy strongly associated with incidence of coronary artery disease[8, 9] and cardiovascular mortality[10, 11]. Such retinal cues could be used to predict future CVD.[12]

The concept of using changes in the retinal vasculature to inform overall CVD risk is certainly attractive and intuitive. However it has not, as yet, translated into routine clinical practice, despite some guidelines suggesting that "risk enhancers" such as the presence of retinopathy could be used to guide initiation of preventative therapy in certain patient groups.[13] Perhaps one of the main reasons for this lack of clinical translation is that the expertise required to assess the retina, particularly quantitively, is limited, and the process itself is of course time-consuming. Software tools have been developed to semi-automate the analysis of the retinal vasculature[14-17] and morphometric measures such as vessel tortuosity, diameter and fractal dimension have again been associated with increased CVD risk in multiple studies.[18-20]

Taking this step further, in this issue, the paper by Rudnicka *et al*.[21] describes the use of a fully automated artificial intelligence (AI)-enabled retinal assessment tool for prediction of CVD risk in two large population cohorts. The software tool, QUARTZ, computes estimates of vessel width, area and tortuosity efficiently. Over 70,000 individuals were included, the majority of whom did not have any prior history of CVD. The authors found that the retinal measurements computed by QUARTZ were significantly associated with CVD (death, myocardial infarction and stroke), with similar

predictive performance to the Framingham clinical risk score. The results strengthen the evidence from several similar studies that the retina can be a useful and potentially disruptive source of information for CVD risk in personalized medicine. As the authors discuss, the accessibility of large repositories of retinal photography does make this concept particularly attractive as it enables validation of hypotheses in large, richly phenotyped cohorts.

So, what next? Beyond demonstrating the association between retinal vascular features and CVD, we must consider how this knowledge could be integrated into clinical care. A number of questions remain.

1. *Who would conduct such a retinal screening programme?* Using retinal screening in this way would presumably require a significant increase in the number of ophthalmologists or otherwise trained assessors. Introducing artificial intelligence would perhaps lessen this burden, although some clinicians may have concerns about the "black box" aspect of machine learning and artificial intelligence technology.[22]
2. *Who would act on any CVD risk findings?* Would ophthalmologists be expected to prescribe preventative CVD therapies, or would cardiologists and primary care practitioners be supported in taking on this additional workload? As with many aspects of modern clinical care, a multi-disciplinary team approach is likely to be optimal. This requires of course a very significant coordination and regulatory effort at national level.
3. *How should the data be translated to clinical practice?* Despite increasing evidence showing that retinal vascular findings can predict CVD risk, the implications of introducing such a screening programme in the general population mean that a higher standard of evidence, i.e., a large, randomised clinical trial, is surely required before the CVD risk prevention guidelines can be changed to incorporate retinal measurements as part of our routine risk prediction assessment. While a one-off retinal measure may be associated with adverse CVD outcome, is this risk modifiable? Observational findings that seemed plausible but did not translate to positive clinical interventional targets abound in the scientific literature. It also seems unlikely that retinal assessment alone could be used as a risk predictor, but it could indeed form part of a comprehensive CVD risk assessment incorporating other clinical risk factors. Even using AI, in this study by Rudnicka *et al.*[21] around 20% of the images were not of sufficient quality to be assessed using QUARTZ.

Looking to the future, there have been numerous studies reporting consistent associations between retinal vascular parameters and CVD prognosis. The retina may indeed provide a rich source of prognostic information relating to CVD risk. What is now needed is for ophthalmologists, cardiologists, primary care physicians and computer scientists to work together to design studies to determine whether using this information improves clinical outcome, and if so, to work with

regulatory bodies, scientific societies and healthcare systems to optimise clinical workflows and enable practical implementation in routine practice.

The authors report no conflicts of interest.

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