Retinal fingerprints for precision profiling of cardiovascular risk

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Retinal microvascular changes are strongly linked to prevalent and incident cardiovascular disease. These changes can now be mapped with unparalleled accuracy using retinal optical coherence tomography. Novel retinal imaging, combined with the power of deep learning, might soon equip clinicians with unique and precise risk-assessment tools that enable truly individualized patient management.

Cardiovascular disease (CVD) is a leading cause of morbidity and mortality worldwide, partly owing to the increasing prevalence of major risk factors for CVD, such as hypertension, diabetes mellitus and chronic kidney disease. What constitutes CVD has undergone substantial refinement owing to advances in biomarker discovery, analytical chemistry and imaging physics. By contrast, current markers to identify and stratify CVD lack similar precision. These biomarkers are coarse (such as sex and smoking), reflect established target-organ damage (for example, serum creatinine levels and albuminuria) and are unable to discriminate between CVD outcomes (such as blood pressure and LDL-cholesterol levels). Additionally, the capacity of these measures to track the risk of CVD over time or in response to treatment remains poorly defined. Therefore, currently established metrics of the risk of CVD, although useful at a population level, cannot be used to quantify the risk accurately for an individual.

Alterations in the structure and function of microvessels (luminal diameter <300 μm) are a unifying feature in the initiation and progression of CVD. The eye provides a unique window to the microvasculature, and retinal imaging offers a noninvasive method of detecting such alterations that might allow earlier identification and targeting of at-risk patients.

The eye has fascinated artists and scientists for centuries. A future in which retinal scanning is the most reliable biometric means of verifying an individual's identity (and linked history) is closer than many might be comfortable with. These retinal 'fingerprints' rely on the recognition of the unique branching patterns of the retinal vasculature. By contrast, pupillary recognition versions of this technology analyse an individual's corrugations of the iris — the specialized anterior extension of the choroid vascular layer. The vasculature of the eye is, therefore, truly individual and has the potential to yield granular data about burden and risk of CVD.

The eye and CVD

Nearly 80 years ago, the presence of retinopathy was noted to confer an increased risk of adverse outcomes in patients with hypertension. Modern retinal imaging, predominantly using fundus photography, has sought to identify, quantify and link retinal microvascular changes with traditional CVD risk factors and outcomes in different populations. Measures of retinal arteriolar and venular calibre predict the development of hypertension, diabetes and renal impairment as well as CVD complications in patients with coronary artery disease, cerebrovascular disease and diabetes[1]. These metrics also provide incremental value to current CVD risk-stratification tools and have particular utility in predicting outcomes of coronary artery disease in women[1]. Retinal vascular geometry and network complexity have been analysed to identify subtle or evolving vessel pathology, showing associations with prevalent CVD risk factors and events.

Barriers to the translation of retinal imaging to clinical practice as part of CVD risk assessment, such as lack of automated metrics, magnification or focusing errors and the need for mydriasis (dilatation of the pupil) for static vessel analysis, have been overcome with advances in imaging hardware and analysis software. The ease of imaging the retinal circulation is an important strength but misrepresents the true depth of the eye's microvasculature. The use of novel imaging modalities, such as retinal optical coherence tomography (OCT), to target deeper retinal vascular networks, which might reflect microvascular disease earlier and more accurately, can overcome this challenge.

Deep imaging with retinal OCT

Retinal OCT provides rapid, ultra-high resolution, tomographic (cross-sectional) imaging of the retina in near-histological detail. Identification and automated segmentation of individual retinal layers with the use of OCT has provided novel insights into the role of the chorioretinal microvasculature in the pathogenesis

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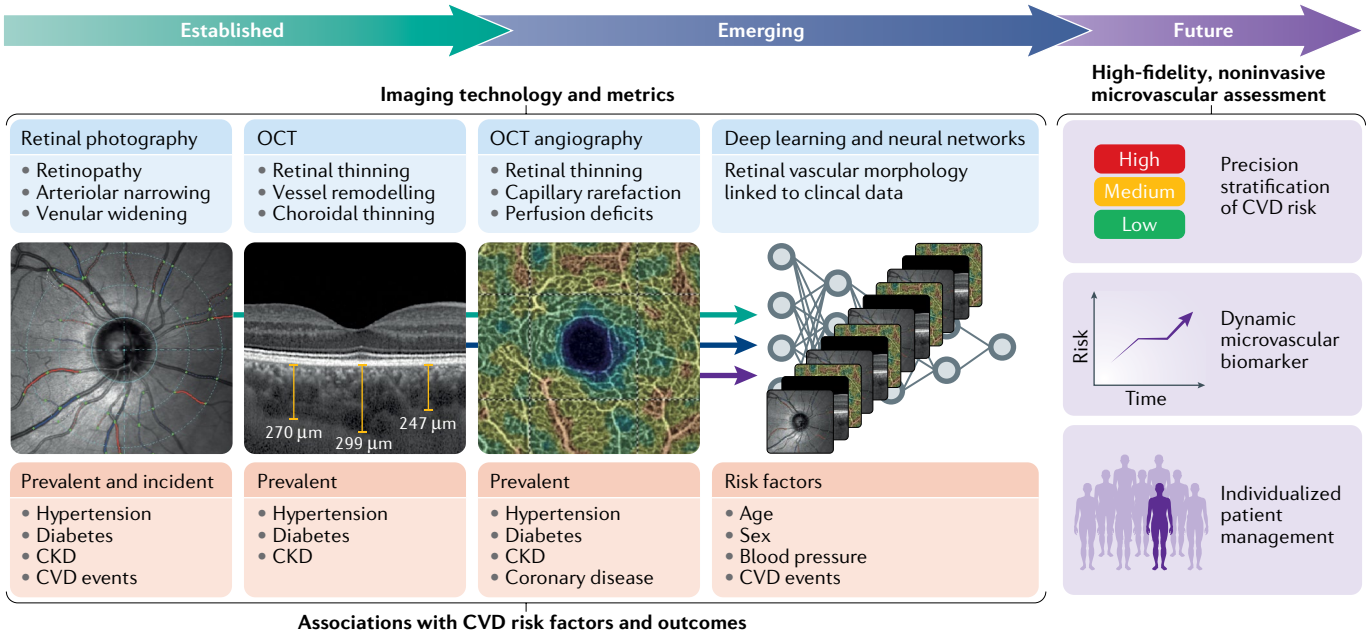

Fig. 1 | **Retinal fingerprints for precision profiling of the risk of cardiovascular disease.** Multimodal imaging enables the comprehensive assessment of the retinal microvasculature to define the risk of cardiovascular disease (CVD). Changes in vessel calibre and network geometry observed by retinal photography are strongly associated with CVD risk factors and outcomes. Novel retinal metrics associated with risk of CVD, such as chorioretinal thinning and capillary rarefaction, are emerging following the advent of optical coherence tomography (OCT) and its contrast-free angiography platform. Integration of these high-fidelity imaging data with machine learning analysis and neural network formation represents the next critical phase in developing retinal imaging as a means of providing individualized assessment of the risk of CVD. CKD, chronic kidney disease.

of age-related macular degeneration, diabetic retinopathy and glaucoma. OCT also has the potential to image the previously inaccessible choroid. This layer contains the choroidal circulation, which receives ~80% of retinal blood flow and provides passive oxygenation of important visual apparatus, including the retinal pigment epithelium, photoreceptors and the avascular fovea. The cross-sectional nature of OCT imaging allows vessel wall and/or lumen analyses but OCT also acquires en-face fundus images for vessel calibre assessment to complement choroidal imaging. Therefore, OCT captures the entire chorioretinal microcirculation and its dependent tissue in a single platform.

OCT has revealed vessel remodelling and chorioretinal thinning in clinical hypertension, diabetes and chronic kidney disease. The highly vascular nature of the choroid suggests that this thinning probably represents changes in microvascular structure or function. We have found that choroidal thinning was more severe in individuals with a lower glomerular filtration rate and greater proteinuria, both strongly associated with microvascular dysfunction[2]. Also, those with a thinner choroid had higher serum levels of endothelin 1 and asymmetric dimethylarginine (an endogenous inhibitor of nitric oxide synthesis), further supporting this association. Importantly, we linked chorioretinal thinning with renal histological vascular injury, demonstrating that OCT-derived metrics can inform on changes in distant target organs[2]. Choroidal thinning is also seen in patients with overt CVD, but no data currently exist on its utility for profiling the risk of CVD compared with standard clinical measurements.

OCT angiography combines structural and functional imaging by analysing the changing variance over multiple scans in the light speckle created by erythrocyte flow. This approach generates a contrast-free retinal angiogram down to the capillary level and surrogate indices of perfusion. Data are emerging showing reduced retinal vessel density and perfusion in individuals with CVD risk factors as well as in those with overt CVD. One study found correlations between the severity of retinal capillary rarefaction and greater risk of CVD, assessed using the AHA and Global Registry for Acute Coronary Events (GRACE) scoring systems[3]. Of note, OCT angiography is susceptible to movement artefact degradation and lacks true perfusion indices. The latter problem can be overcome with the addition of Doppler OCT, which detects the frequency shift of back-scattered light from erythrocyte flow, allowing determination of blood-flow velocity together with vessel dimensions.

Preclinical OCT allows simultaneous, noninvasive longitudinal imaging of the eye in disease models and might provide novel insights into underlying mechanisms. We have used OCT to explore the links between the eye and the kidney and have shown that mice with hypertension alone had no choroidal thinning, whereas mice with matched hypertension levels and additional renal injury developed significant choroidal thinning[2]. These studies are important to advance our understanding of the retinal vascular changes associated with systemic vascular disease.

Deep learning and retinal imaging

Deep learning is an extension of machine learning whereby predictive patterns are learnt and refined by the machine itself, using an algorithm developed from a large example dataset, such as a bank of graded retinal images. Work in this field has used retinal photographs and clinical data from >280,000 patients to train an algorithm to predict a range of risk factors for CVD from two separate banks of retinal photographs, totalling ~13,000 patients[4]. The algorithm had impressive accuracy for predicting sex (area under the curve (AUC) 0.97), smoking status (AUC 0.71), age (mean absolute error ~3 years) and systolic blood pressure (mean absolute error ~11 mmHg)[4]. For predicting incident CVD, the algorithm offered little improvement over a conventional CVD risk-scoring tool, but encouragingly showed equivalent power. A similar approach involving OCT images has been successfully used to triage and diagnose sight-threatening retinal diseases[5].

Future challenges

Important questions remain about the role of retinal imaging in CVD. Do retinal vessel metrics offer sufficient incremental value to clinicians to warrant their inclusion into CVD risk profiling? Data suggest that ~10% of patients are reclassified when adding retinal metrics to current tools[1]. Whether acting on this information translates into meaningful differences in patient outcomes remains unclear. Similarly, whether retinal vascular metrics are modifiable in a manner that enables them to be used as dynamic markers of risk and/or treatment response remains unclear. Addressing these questions will require well-designed preclinical and clinical studies, with longitudinal imaging and data linkage, which are currently available in only a few countries. The continued expansion of analytical technology to maximize the yield from increasingly complex retinal imaging data is an exciting field in itself.

Conclusions

The eye is a well-defined target organ whose microvessel network can now be precisely mapped, measured and tracked. Quantitative vessel analysis of retinal photographs has provided a strong rationale for using retinal fingerprints to report and stratify the risk of CVD (FIG. 1). Novel modalities, such as OCT, have undergone rapid clinical expansion and have shown potential in detecting retinal microvascular changes that are associated with surrogate markers of increased risk of CVD. OCT devices are now commonplace in many opticians, and so the very real potential exists for these devices to be used for CVD risk assessment in the wider community. Advances in data analysis might soon enable clinicians to generate individualized chorioretinal risk scores to identify patients at risk of CVD on the basis of precise, segmented OCT metrics. Combining this deep imaging with deep learning represents the next frontier in defining what the eye can reveal about cardiovascular health and disease.

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Competing interests
The authors declare no competing interests.