



THE UNIVERSITY *of* EDINBURGH

Edinburgh Research Explorer

The eye, the kidney & cardiovascular disease: old concepts, better tools & new horizons

Citation for published version:

Farrah, T, Dhillon, B, Keane, PA, Webb, D & Dhaun, N 2020, 'The eye, the kidney & cardiovascular disease: old concepts, better tools & new horizons', *Kidney International*.
<https://doi.org/10.1016/j.kint.2020.01.039>

Digital Object Identifier (DOI):

[10.1016/j.kint.2020.01.039](https://doi.org/10.1016/j.kint.2020.01.039)

Link:

[Link to publication record in Edinburgh Research Explorer](#)

Document Version:

Version created as part of publication process; publisher's layout; not normally made publicly available

Published In:

Kidney International

General rights

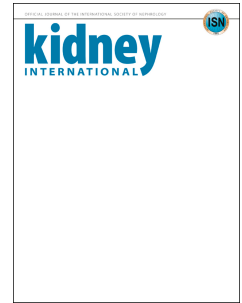
Copyright for the publications made accessible via the Edinburgh Research Explorer is retained by the author(s) and / or other copyright owners and it is a condition of accessing these publications that users recognise and abide by the legal requirements associated with these rights.

Take down policy

The University of Edinburgh has made every reasonable effort to ensure that Edinburgh Research Explorer content complies with UK legislation. If you believe that the public display of this file breaches copyright please contact openaccess@ed.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.



Journal Pre-proof



The eye, the kidney & cardiovascular disease: old concepts, better tools & new horizons

Tariq E. Farrah, BSc MRCP, Baljean Dhillon, FRCS FRCPE FRCOphth, Pearse A. Keane, MSc FRCOphth MRCSI, David J. Webb, DSc FRCP, Neeraj Dhaun, PhD FRCP

PII: S0085-2538(20)30216-7

DOI: <https://doi.org/10.1016/j.kint.2020.01.039>

Reference: KINT 1969

To appear in: *Kidney International*

Received Date: 10 September 2019

Revised Date: 9 January 2020

Accepted Date: 13 January 2020

Please cite this article as: Farrah TE, Dhillon B, Keane PA, Webb DJ, Dhaun N, The eye, the kidney & cardiovascular disease: old concepts, better tools & new horizons *Kidney International* (2020), doi: <https://doi.org/10.1016/j.kint.2020.01.039>.

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Copyright © 2020, Published by Elsevier, Inc., on behalf of the International Society of Nephrology.

**The eye, the kidney & cardiovascular disease:
old concepts, better tools & new horizons**

Tariq E Farrah BSc MRCP^{1,2}

Baljean Dhillon FRCS FRCPE FRCOphth^{3,4}

Pearse A Keane MSc FRCOphth MRCSI⁵

David J Webb DSc FRCP¹

Neeraj Dhaun PhD FRCP^{1,2}

¹University/BHF Centre for Cardiovascular Science, The Queen's Medical Research Institute, University of Edinburgh, Edinburgh, UK.

²Department of Renal Medicine, Royal Infirmary of Edinburgh, Edinburgh, UK

³Centre for Clinical Brain Sciences, University of Edinburgh, Edinburgh, UK

⁴Princess Alexandra Eye Pavilion, Edinburgh, UK

⁵NIHR Biomedical Research Centre for Ophthalmology, Moorfields Eye Hospital, London, UK

Correspondence to: Dr Neeraj Dhaun
Centre for Cardiovascular Science
The Queen's Medical Research Institute
47 Little France Crescent, Edinburgh.
E-mail: bean.dhaun@ed.ac.uk

Short title: Retinal imaging & the kidney

Abstract word count:	222	Main article word count:	5,762
Tables:	4	Figures:	5
Supplementary tables:	3	Supplementary figures:	5
Supplementary videos	4	References	159
Pages:	56		

Abstract

Chronic kidney disease (CKD) is common with hypertension and diabetes mellitus acting as major risk factors for its development. Cardiovascular disease is the leading cause of death worldwide and the most frequent endpoint of CKD. There is an urgent need for more precise methods to identify patients at risk of CKD and cardiovascular disease. Alterations in microvascular structure and function contribute to the development of hypertension, diabetes, CKD and their associated cardiovascular disease. Homology between the eye and kidney suggest that non-invasive imaging of the retinal vessels can detect these microvascular alterations to improve targeting of at-risk patients. Retinal vessel-derived metrics predict incident hypertension, diabetes, CKD and cardiovascular disease and add to current renal and cardiovascular risk stratification tools. The advent of optical coherence tomography (OCT) has transformed retinal imaging by capturing the chorioretinal microcirculation and its dependent tissue with near-histological resolution. In hypertension, diabetes and CKD, OCT has revealed vessel remodelling and chorioretinal thinning. Clinical and pre-clinical OCT have linked retinal microvascular pathology to circulating and histological markers of injury within the kidney. The advent of OCT angiography allows contrast-free visualisation of intra-retinal capillary networks to potentially detect early, incipient microvascular disease. Combining OCT's 'deep imaging' with the analytical power of deep learning represents the next frontier in defining what the eye can reveal about the kidney and broader cardiovascular health.

Keywords: chronic kidney disease, hypertension, imaging, microcirculation, ocular, proteinuria

Abbreviations

AVR – arteriole-to-venule ratio

BP – blood pressure

CKD – chronic kidney disease

CRAE – central retinal arteriolar equivalents

CRVE – central retinal venular equivalents

CVD – chronic kidney disease

D_f – fractal dimension

eGFR – estimated glomerular filtration rate

ESRD – end stage renal disease

OCT – optical coherence tomography

OCT-A – optical coherence tomography angiography

GCL – ganglion cell layer

GBM – glomerular basement membrane

Introduction

Chronic kidney disease (CKD) affects ~10% of the world's population and its incidence is increasing.¹ Hypertension and diabetes mellitus are also common worldwide with an estimated prevalence of ~30% and ~10%, respectively; both are important risk factors for the development and progression of CKD.^{2, 3} These systemic diseases are strongly associated with incident cardiovascular disease (CVD) and their inter-relationship contributes to CVD being the most common endpoint of CKD.⁴ Current clinical tools lack precision to detect, stratify and track individual patients at increased risk of progressive CKD and CVD, and prior to end-organ damage. Thus, there is an urgent unmet need for simple, non-invasive methods to allow earlier identification and risk stratification of patients at increased risk of progressive end-organ injury and subsequent end-stage renal disease (ESRD) and CVD.

Microvessels (luminal diameter <300 μm) regulate tissue perfusion and contribute to systemic vascular resistance. This ability is closely linked to endothelial function. Several pathophysiological processes may contribute to *and* be a consequence of endothelial dysfunction, with downstream effects on microvessels (**Figure 1**).⁵ Alterations in microvascular structure and function contribute to the development and progression of hypertension, diabetes, CKD and CVD.⁵⁻⁷ Importantly, such changes precede the development of end-organ damage⁸ and appear modifiable.⁹ Moreover, microvascular dysfunction in peripheral beds mirrors dysfunction in visceral beds,^{10, 11} providing a rationale for imaging accessible microvessels, such as those of the eye. Transparency of the ocular media allows direct visualisation of the microvasculature that may be affected by systemic diseases such as hypertension, diabetes and CKD. Here, we discuss the basis for the eye to act as a window to the kidney and evidence for the microcirculation of the eye to report risk of adverse renal and CVD outcomes.

The eye as a window to the kidney

The eye and kidney have several structural, developmental and organisational similarities that support the concept that ocular tissues might reflect renal disease (**Figure 2**).

Bruch's membrane and the glomerular basement membrane

Bruch's membrane divides the posterior pole of the eye into the retina (a laminated neurovascular structure) and choroid (an almost entirely vascular structure), collectively termed chorioretinal. Bruch's membrane and the glomerular basement membrane (GBM) both contain a network of $\alpha 3$, $\alpha 4$ and $\alpha 5$ type IV collagen chains.^{12, 13} Thus, inherited or acquired diseases involving type IV collagen can affect both organs; the presence of co-existent nephropathy and retinopathy in Alport syndrome is a well-described example of this (**Supplementary figure 1**).^{14, 15} Another example, anti-GBM disease is characterised by the development of immunoglobulin-G autoantibodies directed against the $\alpha 3$ chain, which are deposited on glomerular and alveolar basement membranes triggering a crescentic glomerulonephritis and pulmonary haemorrhage, respectively.¹⁶ Similar linear immunoglobulin-G deposition in Bruch's membrane has been reported in patients with anti-GBM disease who developed concurrent choroidal ischaemia and retinal detachment.^{17, 18}

The arrangement of the choroidal capillary (choriocapillaris) endothelium, Bruch's membrane and the retinal pigment epithelium mirrors that of the glomerular endothelium, GBM and podocyte (**Figure 2**). The pathological relevance of this homology is readily appreciated in membrano-proliferative glomerulonephritis type II in which electron dense deposits are found on the GBM and on Bruch's membrane.¹⁹ Evidence of complement system dysregulation as a key driver of renal and retinal deposit formation in membrano-proliferative glomerulonephritis²⁰ and drusen deposition on Bruch's membrane in age-related

macular degeneration has extended the link between eye and kidney to include immune regulation.^{21, 22}

Chorioretinal and renal microcirculations

Development and ultrastructure

The human retinal circulation develops predominantly by angiogenesis, where new vessels bud from pre-existing ones, to supply the inner two-thirds of the retina.²³ In the kidney, the peritubular capillaries and vasa recta populate the medulla and inner cortex in a similar manner.²⁴ In contrast, the choroidal and glomerular endothelium are reported to develop by vasculogenesis, where clusters of progenitor cells form islands of *de novo* vessels giving rise to the choriocapillaris and renal corpuscle respectively,^{24, 25} although for the glomerulus this is debated.²⁶ The choriocapillaris endothelium has ~80 nm fenestrations allowing fluid exchange within the subretinal space.²⁷ The glomerular endothelium has similarly sized fenestrations that facilitate ultrafiltration into Bowman's capsule.²⁸

Organisation and blood flow

The retinal and medullary circulations each receive <20% of the total ocular and renal blood flow, respectively, despite the high metabolic activity of the retinal photoreceptors and the medullary counter-current exchange system. Thus, both regions have a lower oxygen tension compared to their choroidal and cortical counterparts creating matched chorioretinal and corticomedullary oxygen gradients (**Figure 2**). The choroidal circulation receives ~80% of ocular blood flow and passively oxygenates key visual apparatus including the pigment epithelium and photoreceptors particularly within the avascular fovea.²⁵ This role demands a blood flow that is 4-fold higher *per* unit mass than the kidney and 10-fold higher than the brain,²⁵ indicating the importance of the choroid to global retinal health. Choroidal vascular

change may therefore predate the onset of overt retinopathy and, if detectable, might allow earlier identification of incipient disease.

Regulation of blood flow

All components of the renin-angiotensin-aldosterone system are widely expressed throughout the retinal and choroidal vascular networks (**Figure 2**).²⁹ Similar to effects in the kidney, angiotensin II acting *via* type I receptors leads to chorioretinal vasoconstriction³⁰ but may also modulate glial-pericyte-vasomotor signalling that maintains retinal neurovascular integrity.³¹ Excessive renin-angiotensin-aldosterone system activation contributes to the pathogenesis of diabetic retinopathy and both diabetic and non-diabetic CKD.³² Moreover, renin-angiotensin-aldosterone system inhibition in clinical trials prevents the development and progression of diabetic retinopathy and nephropathy, probably independently of effects on blood pressure (BP).³²

Within the eye, endothelin-1 (ET-1) mediates vasoconstriction *via* endothelin-A (ET_A) receptors which are predominantly localised to choroidal and retinal vascular smooth muscle cells. In contrast, endothelin-B (ET_B) receptors appear confined to neuronal and glial structures.³³ Similarly in the kidney, ET_A receptors are localised to the vascular smooth muscle of glomeruli and vasa recta, whereas ET_B receptors are mainly localised to the collecting system (**Figure 2**). Selective ET_A receptor blockade in the eye increases retinal blood flow and reduces both retinal pericyte apoptosis and retinal thinning in a mouse model of type 2 diabetes.³⁴ These effects are mirrored in the kidney where selective ET_A blockade ameliorates intra-glomerular hypertension, podocytopathy and fibrosis to slow CKD progression.^{35, 36} Autonomic innervation in the eye is limited to the choroidal circulation where sympathetic activation mediates choroidal vasoconstriction²⁵ in a similar manner to effects on intra-renal vessels. Thus, the choroidal microvasculature, rather than retinal

vessels, may more accurately reflect the renal microvasculature, particularly in diseases characterised by excessive sympathetic activation, such as CKD.¹

Retinal imaging, the kidney and cardiovascular disease

Retinal photography

Qualitative retinopathy grading (for example microaneurysms, haemorrhages or focal arteriolar narrowing) and computer-assisted quantitative retinal vessel calibre analysis of digital fundus photographs have been the mainstay of retinal imaging for the last 20 years (**Supplementary figure 2**). As retinopathy reflects established end-organ damage detecting changes in retinal vessel calibre that precede this overt damage may allow earlier identification of at-risk patients.³⁷ The most established metrics are derived from arteriolar and venular widths from vessels close to the optic disc (**Table 1 & Supplementary figure 2**). Novel indices of retinal vascular network geometry such as fractal dimensions (Df) can be derived from skeletonised vessel maps from retinal photographs (**Figure 3**). These indices identify suboptimal vascular branching patterns that may reflect and promote microvascular damage in systemic disease.^{38, 39} The presence and severity of retinopathy, vessel calibre change and fractal deviations have been strongly linked to hypertension, diabetes mellitus and CKD as well as CVD endpoints.

The retinal circulation - CVD risk factors and outcomes

Hypertension

Retinal arteriolar narrowing is thought to reflect increased systemic vascular tone. Large cross-sectional studies demonstrate strong, independent associations between BP and generalised and focal arteriolar narrowing.⁴⁰ Longitudinal studies have shown that retinal arteriolar narrowing is associated with a ~2-fold increased risk of incident hypertension independent of age, sex, baseline BP and other CVD risk factors (**Supplementary table 1**),

supporting the concept that retinal microvascular changes precede overt disease and are able to identify at-risk individuals. This paradigm has been challenged more recently by data suggesting a high prevalence of masked hypertension at the time of retinal imaging as detected by ambulatory BP monitoring.⁴¹ Additionally, systolic BP and mean arterial pressure show an inverse linear relationship with Df in keeping with rarefaction.⁴²⁻⁴⁴ This relationship holds true in young children with a normal BP (a population who should lack confounding pre-existing vascular risk factors) and is independent of retinal arteriolar calibre.⁴⁵

Diabetes mellitus

Diabetic retinopathy is associated with systemic vascular complications likely reflecting widespread microvascular disease.⁴⁶ More so than in hypertension, retinal venular widening is prevalent in diabetes, correlates with severity of retinopathy and predicts progression to overt retinopathy suggesting a different pathophysiological basis for the change in vessel calibre.⁴⁷ Wider venules are seen in response to chronic hypoxia⁴⁸ and associate with endothelial dysfunction,⁴⁹ suggesting they reflect microvascular stress in response to metabolic derangement. In support of this concept, higher cholesterol, greater body mass index and worse glycaemic control link to wider retinal venules.⁵⁰⁻⁵³ Moreover, wider venules and smaller AVR predict incident fasting hyperglycaemia and diabetes over 5 to 10 years, independent of fasting glucose, insulin levels, body mass index, family history or BP (**Supplementary table 2**).⁵⁴ Finally, reduced Df in those with diabetes can predict incident neuropathy, nephropathy and progressive retinopathy independent of other risk factors for microvascular complications although the strength of these associations is modest.^{55, 56}

CKD

Retinopathy (diabetic, hypertensive or otherwise) is more prevalent in patients with CKD, independent of standard CVD risk factors including diabetes and proteinuria.⁵⁷ Retinopathy

severity also shows a graded relationship with declining estimated glomerular filtration rate (eGFR) and its presence predicts future decline in renal function.^{58, 59} Analysis of ~1000 patients from Chronic Renal Insufficiency Cohort with serial fundus photographs found that progressive retinopathy also tracks CKD progression in a subgroup of patients.⁶⁰ However, these initial associations were lost after adjusting for baseline risk factors for progression suggesting little added benefit of retinal metrics.⁶⁰ Both arteriolar narrowing and venular widening have been associated with prevalent CKD⁶¹ but whether retinal vessel calibres predict incident or progressive CKD is not clear (**Table 2**). The Atherosclerosis Risk in Communities study examined retinal photographs of ~10,000 middle-aged patients and showed that those in the lowest AVR quintile had the greatest increase in serum creatinine over a six-year period; this held true after adjusting for baseline vascular risk factors.⁵⁹ Analysis of retinal images from ~4,500 patients without baseline CKD from the Multi-Ethnic Study of Atherosclerosis study found that narrower arterioles predicted the development of CKD in white patients alone.⁶⁵ However, other large, well designed studies have failed to find an independent association between any vascular calibre metric and CKD progression.^{61,}

64

Albuminuria, an established marker of renal microvascular injury and an independent risk factor for CKD progression and incident CVD,¹ may better reflect retinal vascular changes. Cross-sectional studies have shown that a narrower CRAE is independently associated with greater albuminuria⁷¹ and more severe glomerulopathy on histology in early diabetic CKD,⁷² linking retinal and renal microvascular pathology. Additionally, baseline and subsequent arteriolar narrowing predicts worsening albuminuria and histological disease progression as well as decline in eGFR in both diabetic and non-diabetic CKD.^{62, 66, 72} Importantly, using CRAE in conjunction with albuminuria allowed better stratification of individuals at increased risk of CKD progression than albuminuria alone.⁶⁶

Studies exploring fractals in CKD are few and conflicting. A small study from Singapore (n=260) found a modest U-shaped relationship between *Df* and CKD, suggesting that *increased* vascular branching complexity, potentially due to neovascularisation as is often seen in diabetic retinopathy, is also indicative of increased risk.⁷³ A larger Malay study (n=3280) subsequently found lower *Df* to be strongly associated with lower eGFR and heavier proteinuria.⁷⁴ In contrast, large studies of both diabetics and non-diabetics found no relationship between either baseline or change in *Df* and the presence or progression of CKD (**Table 2**)^{70, 75}

The lack of a consistent retinal vascular metric for the detection of incident and prevalent CKD may reflect the heterogeneity of the study populations, underlying aetiologies, metabolic abnormalities and treatments, such as immunosuppression and erythropoietin-stimulating agents. It may also suggest that retinal photography has limited sensitivity to reveal a reliable metric amongst these competing influences.

CVD outcomes

Retinal arteriolar narrowing, in contrast to venular widening, shows greater associations with atherothrombotic rather than metabolic CVD risk factors,⁵³ but both link to CVD outcomes. Large epidemiological studies and meta-analyses have shown that retinopathy, narrower arterioles and wider venules are common in patients with known ischaemic stroke disease.⁷⁶⁻⁷⁸ Moreover, their presence predicts incident ischaemic stroke and stroke mortality, independent of other baseline CVD risk factors (**Supplementary table 3**).⁷⁹⁻⁸¹ These same metrics are also independent predictors of atherosclerotic coronary artery disease morbidity and mortality, which appear stronger for women than men (**Supplementary table 3**).^{82, 83} A lower *Df* showed a linear relationship with worsening severity of coronary vessel stenosis in

~1,700 patients with ischaemic heart disease⁸⁴ and also associated with prevalent stroke.⁸⁵ In large prospective studies, a suboptimal *Df* conferred a 40% increased risk of stroke over a 5 year period⁸⁶ and a 50% increased risk of death from coronary artery disease over a 14-year period (**Supplementary table 3**).⁸⁷ These analyses included adjustment for standard CVD risk factors and retinal vessel calibres suggesting a better predictive ability of *Df*.⁸⁷

The presence of retinal microvascular disease may also stratify patients at future risk of CVD as demonstrated by a recent study of >3,500 patients with microalbuminuria. Here, a wider CRVE predicted incident CVD over six years.⁸⁸ Furthermore, the presence of a single retinal microvascular abnormality, in conjunction with microalbuminuria, increased the risk of incident CVD 2-fold, and this rose to >6-fold if multiple vascular abnormalities were present.⁸⁸ Finally, and importantly, the use of retinal vascular metrics such as arteriolar narrowing and venular widening can provide added benefit over current atherosclerotic CVD risk prediction tools as demonstrated for ischaemic stroke⁸¹ and coronary artery disease.⁸⁹

These data provide robust evidence of the potential clinical utility of retinal imaging-based CVD risk assessment. Transition into clinical practice is still awaited and may have been hindered by inherent limitations (**Table 1**). The use of novel imaging modalities to target deeper vascular networks such as the choroidal circulation, which may reflect microvascular disease earlier and more accurately, might overcome some of these challenges. This is now possible through retinal optical coherence tomography (OCT).

Retinal OCT

Retinal OCT provides high-resolution, tomographic (cross-sectional) imaging of the eye with near histological detail.⁹⁰ The advent of retinal OCT has transformed clinical ophthalmology. In 2010, an estimated 16 million OCT scans were performed in the United States alone, more

than all other ocular imaging combined.⁹¹ This rapid expansion has provided novel insights into the role of the chorioretinal microvasculature in the pathogenesis of age-related macular degeneration, diabetic retinopathy and glaucoma, eye diseases that have an increased prevalence in CKD.⁶¹ The technical principles underpinning OCT are analogous to those of ultrasound but measure light reflections rather than the sound echoes (**Supplementary figure 3**). The measurement of small variations (interference) in light waves over short distances is made possible through the use of interferometry. In current generations of OCT, a Fourier transform analyses multiple interference signals simultaneously *via* a spectrometer (spectral domain OCT) or a tuneable laser (swept source OCT) resulting in extremely fast image acquisition.⁹⁰ Swept source OCT may also provide better tissue penetration than spectral domain OCT allowing better identification of deep structures like the choroid.⁹²

The ultra-high resolution (typically 2-8 μ m) of OCT allows identification and automated segmentation of retinal layers providing measures of global and regional retinal thickness, volume and nerve fibre layer thickness allowing detection of retinal neurodegeneration. (**Table 3, Figure 4, Supplementary figure 4, videos 1 & 2**).⁹⁰ Importantly, OCT devices are capable of eye-tracking and image co-registration for accurate longitudinal imaging. Another key strength of OCT is the potential to image the previously inaccessible choroid, which is almost entirely composed of the blood vessels of the choroidal circulation (**Figure 4**). OCT-derived metrics of choroidal structure have been shown to be reproducible, correlate well with histology and may be surrogate measures for microvascular density with thinning suggestive of rarefaction.⁹³⁻⁹⁵ In addition, the cross-sectional nature of the OCT image allows vessel wall/lumen analyses. OCT devices can also acquire *en-face* retinal images for vessel calibre assessment to complement choroidal imaging (**Supplementary figure 2**).⁹⁶ In short,

OCT allows comprehensive structural assessment of the entire chorioretinal circulation and its dependent tissue *in vivo* within a single platform.

The chorioretinal circulation: CVD risk factors and outcomes

Hypertension

We have used OCT to prospectively examine chorioretinal thickness in patients with established hypertension and age- and sex-matched healthy subjects.⁹⁷ We excluded patients with a history of eye disease, diabetes, or overt CVD. We found no differences in OCT metrics between these carefully matched groups. Two larger studies have produced contrasting results. The Beijing Eye study imaged ~3,000 adults and reported small increases in choroidal thickness with increasing diastolic BP but not systolic BP.⁹⁸ Paradoxically, the presence of hypertension was characterised by choroidal thinning. A subsequent cross-sectional study from Korea found that patients with hypertension (n=140) had significant retinal thinning in nearly all regions assessed compared to those without hypertension (n=687).⁹⁹ Notably the hypertensive group was older with a greater prevalence of CVD risk factors. More recently, a single centre study from Italy of 100 patients with hypertension found consistent retinal and choroidal thinning in hypertensives with co-existent CKD (defined by an eGFR <60 ml/min/1.73m² and/or moderate albuminuria) compared to hypertensives with preserved renal function.¹⁰⁰ These differences persisted following adjustments for age, antihypertensive use and glycaemia. The lack of a matched healthy control group in this otherwise well-designed study limits wider generalisability to CVD risk.

OCT also enables cross-sectional assessment of retinal vessels. Muraoka *et al* reported a greater arteriolar and venular wall thickness in 106 hypertensive patients compared to 132 patients without hypertension.¹⁰¹ Given lumen size remained normal, their findings suggested outward vascular remodeling.

Interpreting the broader significance of these contrasting results in hypertension is difficult as different ethnic groups were studied, imaging devices varied, medication and comorbidity data were inconsistently reported, and those with diabetes were variably included. Large prospective studies that take such factors into account are needed to clarify any relationship and explore causality.

Diabetes mellitus

Studies using OCT to assess retinal thickness between patients with and without diabetes overall have shown significant thinning of the nerve fibre and ganglion cell layers even when retinopathy is absent or mild.^{102, 103 104} Retinal ganglion cells are interneurons that transmit visual information from photoreceptor cells to the visual cortex via the optic nerve. Ganglion cell apoptosis is an early hallmark of retinal neurodegeneration which manifests as thinning of the ganglion cell layer (GCL) on OCT.¹⁰⁵ Such GCL thinning is not observable by standard retinal photography or scanning laser ophthalmoscopy.¹⁰⁵ Studies using OCT in types 1 and 2 diabetes, with no or minimal clinically observable retinopathy, have found selective GCL thinning compared to health.^{102, 103} The degree of thinning correlates highly with duration of type 1 diabetes.¹⁰² Studies of the choroid also show that patients with diabetes have thinner choroids compared to age- and sex-matched controls, even in the absence of retinopathy.^{106, 107} Recent work suggests that greater reductions in choroidal thickness and choroidal vascular density occur with worsening retinopathy in keeping with progressive microvascular damage.¹⁰⁸ Whether the choroidal thinning contributes to, or indeed is a result of, retinal vascular disease needs further study. The choroid may therefore reflect early systemic vascular changes in diabetes such as glomerular hyperfiltration and hypertension.

Pre-dialysis CKD

We showed, for the first time, that patients with varying degrees of non-diabetic, pre-dialysis CKD exhibit ~5% retinal and ~25% choroidal thinning compared to both age- and sex-matched healthy subjects and patients with hypertension (**Figure 4**).⁹⁷ The highly vascular nature of the choroid suggests that thinning here is likely to represent changes in microvascular structure or function. Supporting this, we found that the choroid was thinner in those with a lower eGFR and greater proteinuria, both strongly associated with microvascular dysfunction.^{109, 110} Also, those with a thinner choroid had higher circulating ET-1 and plasma asymmetric dimethylarginine (an endogenous inhibitor of nitric oxide synthesis) further supporting this association. Importantly, we linked chorioretinal thinning with renal histology, showing that the severity of glomerular injury reflected the degree of choroidal thinning. Recent data using different OCT platforms have confirmed our results. The previously discussed Italian study found that lower eGFR and greater microalbuminuria were associated with choroidal thinning using swept source OCT in 100 hypertensive patients.¹⁰⁰ Moreover, with respect to eGFR, this association was independent of age and other vascular risk factors.¹⁰⁰ These results are interesting as eGFR was preserved (~ 70 ml/min/1.73m²) and proteinuria was low suggesting only modest microvascular damage. This contrasts with our work where CKD patients had moderate-to-severe renal disease (mean eGFR ~ 37 ml/min/1.73m², proteinuria equivalent to ~ 2 g/day).⁹⁷ Another recent study included patients with more advanced CKD and found a consistent relationship between lower eGFR, greater protein leak and a thinner choroid.¹¹¹ The differences in OCT metrics between CKD, hypertension and health, as well as their associations with CKD severity, provide initial evidence for the potential of OCT to identify and stratify individuals at increased CVD risk. Whether these metrics reflect systemic microvascular damage better than standard tools should be tested in future studies. Finally, the consistency of these findings across different

OCT devices using different technology and segmentation algorithms at least supports the fidelity of the relationship. Studies exploring whether this relationship can predict CKD outcomes are awaited.

ESRD

CVD risk is greatest in those with ESRD and on maintenance dialysis.¹ Haemodialysis is associated with repetitive subclinical myocardial injury, which has been linked to microvascular dysfunction that likely contributes to this risk.¹¹² A simple, non-invasive method of assessing microvascular disease in this very high-risk group would be useful. In keeping with our data, studies have shown that dialysis patients have global retinal thinning compared to healthy controls.¹¹³ Additionally, a few small clinical studies in these patients have assessed how OCT metrics may be influenced by dialysis *per se* (**Table 4**). Collectively these studies suggest that the choroid, and the retina to a lesser extent, thins following dialysis with the greatest reductions seen patients with diabetic retinopathy. Whether thinning occurs because of changes in BP (altering chorioretinal perfusion), solute clearance, fluid removal or change in intraocular pressure is unclear and the studied cohorts are probably too small and/or heterogenous to assess these relationships in detail. Retinal nerve fibre layer thinning has been associated with neurodegenerative disease such as Alzheimer's disease and Parkinson's disease,¹²⁶ suggesting OCT can act as a window to the brain and cognition. Similar thinning has been found in haemodialysis patients¹²⁵ and supports recent data linking intradialytic cerebral hypoperfusion to progressive cognitive impairment.¹²⁷ There are no robust OCT studies in renal transplant recipients, but the available data suggest retinopathy and nerve fibre layer thinning are common.¹²⁸

CVD outcomes

Studies linking OCT-derived metrics to prevalent CVD are beginning to emerge. Altinkaynak *et al*, studied 56 patients with heart failure with a reduced ejection fraction and found choroidal thinning of ~30% compared to age- and sex-matched healthy controls.¹²⁹ A thinner choroid was strongly associated with a worse ejection fraction in unadjusted analyses, which may reflect choroidal vasoconstriction secondary to reduced cardiac output.¹²⁹ No data on possible confounders such as renal function, diabetic status, CVD risk factors and concomitant drugs were reported.

Choroidal but not retinal thinning has been shown in patients with established coronary artery disease (defined by angiographic coronary artery stenosis, a positive stress test and/or previous coronary revascularisation or myocardial infarction) compared to health in small studies.^{130, 131} However, limited reporting on possible confounding CVD risk factors, the inclusion patients with diabetes and a high CVD risk control group weaken these associations.^{130, 131} A recent study using spectral domain OCT, examined a subgroup of 764 elderly patients (mean age 82 years, two-thirds female) from a French population-based study (>9,000 participants) and found no associations between subfoveal choroidal thickness and previous CVD, current CVD risk factors or estimated future CVD risk according to a clinical scoring tool.¹³² A large amount of missing data, recall bias from patient-declared medical history and a single manual measure of choroidal thickness may have contributed to these negative results.

There are no data linking OCT-metrics to incident CVD to extend the relevance of the associations presented. These data are likely to appear soon and whether OCT-derived metrics can outperform photography-derived metrics for the prediction of CKD and CVD outcomes is an important test of their potential utility. An additional area that warrants exploration is the extent to which retinal OCT metrics are modifiable by interventions such as

lowering BP, reducing proteinuria or restoring kidney function. Such data might allow OCT-derived metrics to be developed from biomarkers into easily assessable surrogate endpoints for clinical trials.

OCT angiography (OCT-A)

Retinal OCT-A combines structural and functional imaging by analysing the changing variance in light speckle created by erythrocyte flow over multiple scans. This generates a contrast-free angiogram down to the capillary level and surrogate indices of perfusion (**Figure 5**).⁹⁰ Most OCT-A platforms have integrated software that automatically segments the OCT images alongside angiographic data to report global and regional vessel density for each retinal layer (**Supplementary figure 5; Supplementary videos 3 & 4**). OCT-A images can be also be used to assess *Df* and the geometry of the foveal avascular zone (FAZ) with widening indicative of capillary drop out (**Figure 5**). Visualisation of these terminal branches of the vascular tree may allow earlier, more precise detection of local and systemic microvascular disease. Small clinical studies of age-related macular degeneration¹³³ and diabetic retinopathy¹³⁴ have used OCT-A to demonstrate novel structural vessel pathology with an apparent reduction in perfusion. Limitations of OCT-A include a susceptibility to movement artefact degradation and a lack of true perfusion indices. Doppler OCT, which detects the frequency shift of back-scattered light from erythrocytes allowing determination of blood flow velocity alongside vessel dimensions, may overcome this latter issue.⁹⁰

Hypertension, diabetes mellitus and CKD

Data supporting a potential role for OCT-A in systemic diseases are emerging. A study of Asian patients with hypertension found that those with poor BP control (assessed by 24h ambulatory monitoring) had a lower deep capillary plexus vessel density compared to those with optimal BP control.¹¹¹ These groups were well matched in terms of age, sex, CVD risk

factors and renal function (mean eGFR ~ 90 ml/min/1.73m²) but the poorly controlled group had greater microalbuminuria.¹¹¹ In adjusted analyses suboptimal BP control, increasing BP and worsening eGFR were associated with worse capillary rarefaction.¹¹¹ An Italian study extended these findings by using OCT-A in 120 hypertensive patients with and without CKD, to report a lower vessel density in both superficial *and* deep capillary plexuses in those with CKD.¹³⁵ The inclusion of patients with more severe renal impairment and heavier proteinuria in this study¹³⁵ may explain the more extensive retinal vessel rarefaction seen compared to the Singapore study.¹¹¹ However, it is important to note different OCT-A devices were used by each centre.

In diabetes, greater FAZ area, lower retinal capillary density and reduced *Df* have been shown to predict progression of diabetic retinopathy.¹³⁶ A recent study using OCT-A has suggested a potential vascular basis for GCL thinning in diabetes.¹³⁷ Patients with no detectable retinopathy, with a short duration of diabetes (~ 8 years) and normal renal function, had significant GCL thinning that was independently associated with lower retinal capillary density and perfusion, suggesting a structural or functional vascular origin.¹³⁷ This hypothesis is countered by pre-clinical and clinical data suggesting that GCL thinning can occur without alterations in histologically-assessed capillary density.¹³⁸ In summary, GCL thinning appears early in diabetes, potentially prior to structural vascular changes but convincingly before overt target organ damage. The earliest functional changes in the diabetic kidney are glomerular hyperfiltration and hypertension.¹³⁹ and detecting this would be useful in guiding intervention and treatment efficacy. Whether GCL thinning or changes in GCL perfusion can act as an early marker of tissue dysfunction in diabetes such as glomerular hyperfiltration and hypertension warrants detailed further study. There are few data in diabetic CKD but a recent

study using OCT-A in 184 patients with type 2 diabetes suggested that a reduced retinal capillary density independently predicted co-existing CKD and its severity.¹⁴⁰

Given the association with risk factors for CKD progression, data linking OCT-A to long term renal outcomes should soon emerge. However, identifying patients at risk of acute kidney injury (AKI) is also important as AKI confers an increased risk of future CKD¹⁴¹ and CVD.¹⁴² OCT-A-derived retinal vessel density was recently shown to predict the risk of contrast-induced AKI following angiography for acute coronary syndrome.¹⁴³ Moreover, the addition of OCT-A metrics to current contrast-induced AKI risk assessment tools improved prediction of AKI by ~10%.¹⁴³

CVD outcomes

As with OCT, data linking OCT-A metrics to incident CVD are lacking. With respect to prevalent CVD, a study of 246 patients presenting with an acute coronary syndrome found that these patients had reduced inner retinal vessel density compared to a limited number of age- and sex-matched controls.¹⁴⁴ In addition, more severe rarefaction correlated with a greater CVD risk as defined by the *American Heart Association* and *Global Registry for Acute Coronary Events* scoring systems.¹⁴⁴

Dynamic functional imaging

Laser doppler flowmetry and flicker response imaging can assess retinal vascular endothelial function in a dynamic manner. Studies examining laser flicker-induced vascular responses have shown impaired retinal endothelium-dependent vasodilatation in patients with CVD risk factors including albuminuria,¹⁴⁵ pre-diabetes,¹⁴⁶ early hypertension,¹⁴⁷ pre-eclampsia¹⁴⁸ and hypercholesterolaemia.¹⁴⁹ In addition, a recent study reported worsening retinal endothelial function (as measured by the degree of laser flicker-induced vasodilatation) between health,

those at risk of CVD and those with overt CVD,¹⁵⁰ supporting the potential to stratify patients. Limitations of these techniques include the need for mydriasis, longer acquisition time compared to other imaging techniques and assessment of retinal vessels alone.

Visions for the future

Pre-clinical OCT

Pre-clinical OCT allows simultaneous non-invasive longitudinal imaging of the eye in disease models and may provide novel insights into underlying mechanisms. We have used OCT to explore the links between the eye and kidney and shown that mice with hypertension alone had no choroidal thinning whereas mice with matched hypertension but with coexisting renal injury developed significant thinning.⁹⁷ This technology is being refined but has been used to perform detailed structural, functional and biochemical assessments in various models of retinopathy.¹⁵¹

Big data

The recognition of the potential power of OCT beyond eye disease is evidenced by its inclusion in the United Kingdom Biobank study between 2006 and 2010.¹⁵² UK Biobank obtained OCT images from >67,000 participants (of whom >35,000 were healthy) along with socio-demographic, cognitive, CVD and renal risk measures. This could provide novel, robust epidemiological data to establish healthy ranges and generate evidence of OCT metrics as prognostic disease biomarkers. The expansion of OCT out of hospital settings and into the community is already in progress with the leading optometry chain in the United Kingdom announcing a roll out of OCT devices across all outlets.¹⁵³

Deep learning

Machine learning involves programming computers to detect patterns in raw data, based on explicit parameters set by the operator. Such techniques have been utilised to automate classification of diabetic retinopathy from fundus photographs but can be intensive to engineer and supervise. 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.¹⁵⁴ Multiple levels of increasingly abstract pattern recognition enable the algorithm to develop complex neural networks that are highly accurate, require minimal engineering and can match expert human performance as shown recently with diabetic retinopathy.¹⁵⁵

Recent work in this field has used retinal photographs and clinical data from >280,000 patients to train an algorithm to predict a range of CVD risk factors from two separate banks of retinal photographs totalling ~13,000 patients.¹⁵⁶ The algorithm displayed impressive accuracy: gender (AUC 0.97), smoking status (AUC 0.71), age (mean absolute error ~3 years) and systolic BP (mean absolute error ~11 mmHg).¹⁵⁶ For predicting incident CVD risk, the algorithm offered little improvement over a conventional CVD risk-scoring tool but encouragingly showed similar power. More recently, one of the authors of this review (PAK), co-led the development of a deep learning algorithm that allows triage and diagnosis of the commonest sight-threatening retinal diseases from OCT scans.¹⁵⁷ On a large retrospective dataset, this algorithm demonstrated diagnostic accuracy equivalent to that of specialist ophthalmologists. Prospective clinical trials of this algorithm are now planned. Importantly, the algorithm also creates an intermediate representation of the retinal anatomy/pathology and thus addresses, in part, the concerns raised by clinicians regarding artificial intelligence systems which can be often perceived as ‘black boxes’ dictating clinical care. This approach will likely be readily transferable from ophthalmic to systemic disease, offering novel insights and generating new hypotheses.

Challenges

The real-world utility of the retinal vascular metrics for CVD risk profiling over currently available tools is uncertain. Well-designed studies show that such metrics can offer a small benefit (~10%) over current tools in identifying high-risk patients.^{66, 81, 89} Whether this is sufficient for integration into clinical practice is not known nor is how best to act on them. The high fidelity and granular nature of OCT data may yield novel metrics that extend risk stratification beyond what retinal photography has achieved. Pre-clinical and clinical studies with longitudinal imaging and data-linkage, currently available in only a few countries, will be required to confirm this. However, the highly competitive commercial interest in retinal OCT has led to emergence of several devices each with unique retinal layer segmentation algorithms and so metrics are not interchangeable across devices.^{158, 159} Finally, maximising the yield of data from complex OCT and OCT-A images will require similar advancement and investment in imaging analysis methodology which, given the advent of artificial intelligence in healthcare, is an exciting field in itself.

Conclusions

The eye offers a well-defined target organ whose microvessel network is homologous to that in kidney in both health and disease. The chorioretinal microvasculature can now be precisely mapped, measured and tracked. Quantitative vessel analysis of retinal photographs has provided a strong rationale for the eye to report and stratify CVD risk but this is yet to transition into clinical practice. Novel modalities such as OCT have undergone rapid clinical expansion and have shown potential in detecting microvascular changes that are associated with surrogate markers of increased renal and CVD risk. Advances in data analysis and machine learning may soon enable clinicians to generate individualised chorioretinal risk scores to identify patients at risk of adverse outcomes based on precise, segmented OCT

metrics. The advancement of multimodal functional retinal imaging has brought the previously distant goal of non-invasive functional microvascular assessment into sharp focus and the near term.

Acknowledgments

Tariq E. Farrah is supported by a Medical Research Council Clinical Research Training Fellowship. Pearse A. Keane is supported by a NIHR Clinician Scientist Fellowship. Neeraj Dhaun is supported by a British Heart Foundation Intermediate Clinical Research Training Fellowship.

References

1. Gansevoort RT, Correa-Rotter R, Hemmelgarn BR, *et al.*: Chronic kidney disease and cardiovascular risk: Epidemiology, mechanisms, and prevention. *Lancet*, 382: 339-352, 2013.
2. Kearney PM, Whelton M, Reynolds K, *et al.*: Global burden of hypertension: Analysis of worldwide data. *Lancet*, 365: 217-223, 2005.
3. Sarwar N, Gao P, Seshasai SR, *et al.*: Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: A collaborative meta-analysis of 102 prospective studies. *Lancet*, 375: 2215-2222, 2010.
4. Thomas B, Matsushita K, Abate KH, *et al.*: Global cardiovascular and renal outcomes of reduced gfr. *J Am Soc Nephrol*, 28: 2167-2179, 2017.
5. Brunner H, Cockcroft JR, Deanfield J, *et al.*: Endothelial function and dysfunction. Part ii: Association with cardiovascular risk factors and diseases. A statement by the working group on endothelins and endothelial factors of the european society of hypertension. *J Hypertens*, 23: 233-246, 2005.
6. Houben A, Martens RJH, Stehouwer CDA: Assessing microvascular function in humans from a chronic disease perspective. *J Am Soc Nephrol*, 28: 3461-3472, 2017.
7. Stehouwer CDA: Microvascular dysfunction and hyperglycemia: A vicious cycle with widespread consequences. *Diabetes*, 67: 1729, 2018.
8. Halcox JP, Schenke WH, Zalos G, *et al.*: Prognostic value of coronary vascular endothelial dysfunction. *Circulation*, 106: 653-658, 2002.
9. Remuzzi A, Sangalli F, Macconi D, *et al.*: Regression of renal disease by angiotensin ii antagonism is caused by regeneration of kidney vasculature. *J Am Soc Nephrol*, 27: 699-705, 2016.
10. Anderson TJ, Uehata A, Gerhard MD, *et al.*: Close relation of endothelial function in the human coronary and peripheral circulations. *J Am Coll Cardiol*, 26: 1235-1241, 1995.

11. Bonetti PO, Pumper GM, Higano ST, *et al.*: Noninvasive identification of patients with early coronary atherosclerosis by assessment of digital reactive hyperemia. *J Am Coll Cardiol*, 44: 2137-2141, 2004.
12. Booi JC, Baas DC, Beisekeeva J, *et al.*: The dynamic nature of bruch's membrane. *Prog Retin Eye Res*, 29: 1-18, 2010.
13. Boudaud A, Borza D-B, Bondar O, *et al.*: Type iv collagen of the glomerular basement membrane. *J Biol Chem*, 275: 30716-30724, 2000.
14. Savige J, Sheth S, Leys A, *et al.*: Ocular features in alport's syndrome: Pathogenesis and clinical significance. *Clin J Am Soc Nephrol*, 10: 703-709, 2015.
15. Colville D, Savige J, Branley P, Wilson D: Ocular abnormalities in thin basement membrane disease. *Br J Ophthalmol*, 81: 373-377, 1997.
16. McAdoo SP, Pusey CD: Anti-glomerular basement membrane disease. *Clin J Am Soc Nephrol*, 12: 1162-1172, 2017.
17. Jampol LM, Lahov M, Albert DM, Craft J: Ocular clinical findings and basement membrane changes in goodpasture's syndrome. *Am J Ophthalmol*, 79: 452-463, 1975.
18. Rowe PA, Mansfield DC, Dutton GN: Ophthalmic features of fourteen cases of goodpasture's syndrome. *Nephron*, 68: 52-56, 1994.
19. McAvoy CE, Silvestri G: Retinal changes associated with type 2 glomerulonephritis. *Eye*, 19: 985-989, 2005.
20. Sethi S, Fervenza FC: Membranoproliferative glomerulonephritis — a new look at an old entity. *N Engl J Med*, 366: 1119-1131, 2012.
21. Whitmore SS, Sohn EH, Chirco KR, *et al.*: Complement activation and choriocapillaris loss in early amd: Implications for pathophysiology and therapy. *Prog Retin Eye Res*, 45: 1-29, 2015.

22. Dalvin LA, Fervenza FC, Sethi S, Pulido JS: Manifestations of complement-mediated and immune complex-mediated membranoproliferative glomerulonephritis: A comparative consecutive series. *Ophthalmology*, 123: 1588-1594, 2016.
23. Hughes S, Yang H, Chan-Ling T: Vascularization of the human fetal retina: Roles of vasculogenesis and angiogenesis. *Invest Ophthalmol Vis Sci*, 41: 1217-1228, 2000.
24. Sequeira Lopez ML, Gomez RA: Development of the renal arterioles. *J Am Soc Nephrol*, 22: 2156-2165, 2011.
25. Nickla DL, Wallman J: The multifunctional choroid. *Prog Retin Eye Res*, 29: 144-168, 2010.
26. Munro DAD, Davies JA: Vascularizing the kidney in the embryo and organoid: Questioning assumptions about renal vasculogenesis. *J Am Soc Nephrol*, 29: 1593-1595, 2018.
27. Anand-Apte B. HJG: Developmental anatomy of the retinal and choroidal vasculature. In: *Encyclopedia of the eye*. Amsterdam, Elsevier, 2010.
28. Haraldsson B, Nystrom J, Deen WM: Properties of the glomerular barrier and mechanisms of proteinuria. *Physiol Rev*, 88: 451-487, 2008.
29. Wilkinson-Berka JL, Agrotis A, Deliyanti D: The retinal renin-angiotensin system: Roles of angiotensin ii and aldosterone. *Peptides*, 36: 142-150, 2012.
30. Rockwood EJ, Fantes F, Davis EB, Anderson DR: The response of retinal vasculature to angiotensin. *Invest Ophthalmol Vis Sci*, 28: 676-682, 1987.
31. Fletcher EL, Phipps JA, Ward MM, *et al.*: The renin-angiotensin system in retinal health and disease: Its influence on neurons, glia and the vasculature. *Prog Retin Eye Res*, 29: 284-311, 2010.
32. Mauer M, Zinman B, Gardiner R, *et al.*: Renal and retinal effects of enalapril and losartan in type 1 diabetes. *N Engl J Med*, 361: 40-51, 2009.

33. MacCumber MW, D'Anna SA: Endothelin receptor-binding subtypes in the human retina and choroid. *Arch Ophthalmol*, 112: 1231-1235, 1994.
34. Chou JC, Rollins SD, Ye M, *et al.*: Endothelin receptor-a antagonist attenuates retinal vascular and neuroretinal pathology in diabetic mice. *Invest Ophthalmol Vis Sci*, 55: 2516-2525, 2014.
35. Dhaun N, Goddard J, Webb DJ: The endothelin system and its antagonism in chronic kidney disease. *J Am Soc Nephrol*, 17: 943-955, 2006.
36. Heerspink HJL, Parving H-H, Andress DL, *et al.*: Atrasentan and renal events in patients with type 2 diabetes and chronic kidney disease (sonar): A double-blind, randomised, placebo-controlled trial. *Lancet*: 10.1016/S0140-6736(1019)30772-X, 2019.
37. Wong TY, Mitchell P: The eye in hypertension. *Lancet*, 369: 425-435, 2007.
38. Murray CD: The physiological principle of minimum work: I. The vascular system and the cost of blood volume. *Proc Natl Acad Sci U S A*, 12: 207-214, 1926.
39. Patton N, Aslam TM, MacGillivray T, *et al.*: Retinal image analysis: Concepts, applications and potential. *Prog Retin Eye Res*, 25: 99-127, 2006.
40. Cheung CY, Ikram MK, Sabanayagam C, Wong TY: Retinal microvasculature as a model to study the manifestations of hypertension. *Hypertension*, 60: 1094-1103, 2012.
41. Wei FF, Zhang ZY, Thijs L, *et al.*: Conventional and ambulatory blood pressure as predictors of retinal arteriolar narrowing. *Hypertension*, 68: 511-520, 2016.
42. Liew G, Wang JJ, Cheung N, *et al.*: The retinal vasculature as a fractal: Methodology, reliability, and relationship to blood pressure. *Ophthalmology*, 115: 1951-1956, 2008.
43. Cheung CY, Tay WT, Mitchell P, *et al.*: Quantitative and qualitative retinal microvascular characteristics and blood pressure. *J Hypertens*, 29: 1380-1391, 2011.

44. Cheung CY, Thomas GN, Tay W, *et al.*: Retinal vascular fractal dimension and its relationship with cardiovascular and ocular risk factors. *Am J Ophthalmol*, 154: 663-674.e661, 2012.
45. Kurniawan ED, Cheung N, Cheung CY, *et al.*: Elevated blood pressure is associated with rarefaction of the retinal vasculature in children. *Invest Ophthalmol Vis Sci*, 53: 470-474, 2012.
46. Stehouwer CDA: Microvascular dysfunction and hyperglycemia: A vicious cycle with widespread consequences. *Diabetes*, 67: 1729-1741, 2018.
47. 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*, 31: 544-549, 2008.
48. Saldívar E, Cabrales P, Tsai AG, Intaglietta M: Microcirculatory changes during chronic adaptation to hypoxia. *Am J Physiol Heart Circ Physiol*, 285: H2064-H2071, 2003.
49. Nguyen TT, Islam FM, Farouque HM, *et al.*: Retinal vascular caliber and brachial flow-mediated dilation: The multi-ethnic study of atherosclerosis. *Stroke*, 41: 1343-1348, 2010.
50. Ikram MK, de Jong FJ, Vingerling JR, *et al.*: Are retinal arteriolar or venular diameters associated with markers for cardiovascular disorders? The rotterdam study. *Invest Ophthalmol Vis Sci*, 45: 2129-2134, 2004.
51. 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*, 110: 2118-2125, 2003.
52. Klein R, Klein BEK, Moss SE, *et al.*: Retinal vascular caliber in persons with type 2 diabetes: The wisconsin epidemiological study of diabetic retinopathy: Xx. *Ophthalmology*, 113: 1488-1498, 2006.

53. Owen CG, Rudnicka AR, Welikala RA, *et al.*: Retinal vasculometry associations with cardiometabolic risk factors in the european prospective investigation of cancer-norfolk study. *Ophthalmology*, 126: 96-106, 2019.
54. Sabanayagam C, Lye WK, Klein R, *et al.*: Retinal microvascular calibre and risk of diabetes mellitus: A systematic review and participant-level meta-analysis. *Diabetologia*, 58: 2476-2485, 2015.
55. Grauslund J, Green A, Kawasaki R, *et al.*: Retinal vascular fractals and microvascular and macrovascular complications in type 1 diabetes. *Ophthalmology*, 117: 1400-1405, 2010.
56. Cheung CY, Sabanayagam C, Law AK, *et al.*: Retinal vascular geometry and 6 year incidence and progression of diabetic retinopathy. *Diabetologia*, 60: 1770-1781, 2017.
57. Grunwald JE, Alexander J, Maguire M, *et al.*: Prevalence of ocular fundus pathology in patients with chronic kidney disease. *Clin J Am Soc Nephrol*, 5: 867-873, 2010.
58. Grunwald JE, Alexander J, Ying GS, *et al.*: Retinopathy and chronic kidney disease in the chronic renal insufficiency cohort (cric) study. *Arch Ophthalmol*, 130: 1136-1144, 2012.
59. Wong TY, Coresh J, Klein R, *et al.*: Retinal microvascular abnormalities and renal dysfunction: The atherosclerosis risk in communities study. *J Am Soc Nephrol*, 15: 2469-2476, 2004.
60. Grunwald JE, Pistilli M, Ying G-S, *et al.*: Association between progression of retinopathy and concurrent progression of kidney disease: Findings from the chronic renal insufficiency cohort (cric) study. *JAMA Ophthalmol*, 137: 767-774, 2019.
61. Wong CW, Wong TY, Cheng CY, Sabanayagam C: Kidney and eye diseases: Common risk factors, etiological mechanisms, and pathways. *Kidney Int*, 85: 1290-1302, 2014.
62. Wong TY, Shankar A, Klein R, Klein BE: Retinal vessel diameters and the incidence of gross proteinuria and renal insufficiency in people with type 1 diabetes. *Diabetes*, 53: 179-184, 2004.

63. Edwards MS, Wilson DB, Craven TE, *et al.*: Associations between retinal microvascular abnormalities and declining renal function in the elderly population: The cardiovascular health study. *Am J Kidney Dis*, 46: 214-224, 2005.
64. Sabanayagam C, Shankar A, Klein BE, *et al.*: Bidirectional association of retinal vessel diameters and estimated gfr decline: The beaver dam ckd study. *Am J Kidney Dis*, 57: 682-691, 2011.
65. Yau JW, Xie J, Kawasaki R, *et al.*: Retinal arteriolar narrowing and subsequent development of ckd stage 3: The multi-ethnic study of atherosclerosis (mesa). *Am J Kidney Dis*, 58: 39-46, 2011.
66. Baumann M, Burkhardt K, Heemann U: Microcirculatory marker for the prediction of renal end points: A prospective cohort study in patients with chronic kidney disease stage 2 to 4. *Hypertension*, 64: 338-346, 2014.
67. Grunwald JE, Pistilli M, Ying GS, *et al.*: Retinopathy and progression of ckd: The cric study. *Clin J Am Soc Nephrol*, 9: 1217-1224, 2014.
68. Yip W, Sabanayagam C, Teo BW, *et al.*: Retinal microvascular abnormalities and risk of renal failure in asian populations. *PLoS One*, 10: e0118076, 2015.
69. Yip W, Ong PG, Teo BW, *et al.*: Retinal vascular imaging markers and incident chronic kidney disease: A prospective cohort study. *Sci Rep*, 7: 9374, 2017.
70. McKay GJ, Paterson EN, Maxwell AP, *et al.*: Retinal microvascular parameters are not associated with reduced renal function in a study of individuals with type 2 diabetes. *Sci Rep*, 8: 3931, 2018.
71. Awua-Larbi S, Wong TY, Cotch MF, *et al.*: Retinal arteriolar caliber and urine albumin excretion: The multi-ethnic study of atherosclerosis. *Nephrol Dial Transplant*, 26: 3523-3528, 2011.

72. Klein R, Knudtson MD, Klein BE, *et al.*: The relationship of retinal vessel diameter to changes in diabetic nephropathy structural variables in patients with type 1 diabetes. *Diabetologia*, 53: 1638-1646, 2010.
73. Sng CC, Sabanayagam C, Lamoureux EL, *et al.*: Fractal analysis of the retinal vasculature and chronic kidney disease. *Nephrol Dial Transplant*, 25: 2252-2258, 2010.
74. Lim LS, Cheung CY, Sabanayagam C, *et al.*: Structural changes in the retinal microvasculature and renal function. *Invest Ophthalmol Vis Sci*, 54: 2970-2976, 2013.
75. McGowan A, Silvestri G, Moore E, *et al.*: Evaluation of the retinal vasculature in hypertension and chronic kidney disease in an elderly population of irish nuns. *PLoS One*, 10: e0136434-e0136434, 2015.
76. Wong TY, Klein R, Sharrett AR, *et al.*: The prevalence and risk factors of retinal microvascular abnormalities in older persons: The cardiovascular health study. *Ophthalmology*, 110: 658-666, 2003.
77. Cooper LS, Wong TY, Klein R, *et al.*: Retinal microvascular abnormalities and mri-defined subclinical cerebral infarction: The atherosclerosis risk in communities study. *Stroke*, 37: 82-86, 2006.
78. Hughes AD, Falaschetti E, Witt N, *et al.*: Association of retinopathy and retinal microvascular abnormalities with stroke and cerebrovascular disease. *Stroke*, 47: 2862-2864, 2016.
79. Sairenchi T, Iso H, Yamagishi K, *et al.*: Mild retinopathy is a risk factor for cardiovascular mortality in japanese with and without hypertension: The ibaraki prefectural health study. *Circulation*, 124: 2502-2511, 2011.
80. Wang JJ, Liew G, Klein R, *et al.*: Retinal vessel diameter and cardiovascular mortality: Pooled data analysis from two older populations. *Eur Heart J*, 28: 1984-1992, 2007.

81. McGeechan K, Liew G, Macaskill P, *et al.*: Prediction of incident stroke events based on retinal vessel caliber: A systematic review and individual-participant meta-analysis. *Am J Epidemiol*, 170: 1323-1332, 2009.
82. McGeechan K, Liew G, Macaskill P, *et al.*: Meta-analysis: Retinal vessel caliber and risk for coronary heart disease. *Ann Intern Med*, 151: 404-413, 2009.
83. Wong TY, Klein R, Nieto FJ, *et al.*: Retinal microvascular abnormalities and 10-year cardiovascular mortality: A population-based case-control study. *Ophthalmology*, 110: 933-940, 2003.
84. Wang SB, Mitchell P, Liew G, *et al.*: A spectrum of retinal vasculature measures and coronary artery disease. *Atherosclerosis*, 268: 215-224, 2018.
85. Doulal FN, MacGillivray TJ, Patton N, *et al.*: Fractal analysis of retinal vessels suggests that a distinct vasculopathy causes lacunar stroke. *Neurology*, 74: 1102-1107, 2010.
86. Kawasaki R, Che Azemin MZ, Kumar DK, *et al.*: Fractal dimension of the retinal vasculature and risk of stroke: A nested case-control study. *Neurology*, 76: 1766-1767, 2011.
87. Liew G, Mitchell P, Roachchina E, *et al.*: Fractal analysis of retinal microvasculature and coronary heart disease mortality. *Eur Heart J*, 32: 422-429, 2011.
88. Yip W, Sabanayagam C, Ong PG, *et al.*: Joint effect of early microvascular damage in the eye & kidney on risk of cardiovascular events. *Sci Rep*, 6: 27442, 2016.
89. Seidemann SB, Claggett B, Bravo PE, *et al.*: Retinal vessel calibers in predicting long-term cardiovascular outcomes: The atherosclerosis risk in communities study. *Circulation*, 134: 1328-1338, 2016.
90. Keane PA, Sadda SR: Retinal imaging in the twenty-first century: State of the art and future directions. *Ophthalmology*, 121: 2489-2500, 2014.

91. Swanson E, Huang, D: Ophthalmic oct reaches \$1 billion per year: <http://www.octnews.org/articles/2844561/ophthalmic-oct-reaches-1-billion-per-year-but-reim/>. Accessed: July 20th 2018
92. Copete S, Flores-Moreno I, Montero JA, *et al.*: Direct comparison of spectral-domain and swept-source oct in the measurement of choroidal thickness in normal eyes. *Br J Ophthalmol*, 98: 334, 2014.
93. Ramrattan RS, van der Schaft TL, Mooy CM, *et al.*: Morphometric analysis of bruch's membrane, the choriocapillaris, and the choroid in aging. *Invest Ophthalmol Vis Sci*, 35: 2857-2864, 1994.
94. Li XQ, Heegaard S, Kiilgaard JF, *et al.*: Enhanced-depth imaging optical coherence tomography of the human choroid in vivo compared with histology after enucleation. *Invest Ophthalmol Vis Sci*, 57: 371-376, 2016.
95. Shao L, Xu L, Chen CX, *et al.*: Reproducibility of subfoveal choroidal thickness measurements with enhanced depth imaging by spectral-domain optical coherence tomography. *Invest Ophthalmol Vis Sci*, 54: 230-233, 2013.
96. Cameron JR, Ballerini L, Langan C, *et al.*: Modulation of retinal image vasculature analysis to extend utility and provide secondary value from optical coherence tomography imaging. *J Med Imaging*, 3: 020501, 2016.
97. Balmforth C, van Bragt JJ, Ruijs T, *et al.*: Chorioretinal thinning in chronic kidney disease links to inflammation and endothelial dysfunction. *JCI Insight*, 1: e89173, 2016.
98. Wei WB, Xu L, Jonas JB, *et al.*: Subfoveal choroidal thickness: The Beijing eye study. *Ophthalmology*, 120: 175-180, 2013.
99. Kong M, Kwun Y, Sung J, *et al.*: Association between systemic hypertension and macular thickness measured by optical coherence tomography systemic hypertension and macular thickness. *Invest Ophthalmol Vis Sci*, 56: 2144-2150, 2015.

100. Mulè G, Vadalà M, La Blasca T, *et al.*: Association between early-stage chronic kidney disease and reduced choroidal thickness in essential hypertensive patients. *Hypertension Res*, 42: 990-1000, 2019.
101. Muraoka Y, Tsujikawa A, Kumagai K, *et al.*: Age- and hypertension-dependent changes in retinal vessel diameter and wall thickness: An optical coherence tomography study. *Am J Ophthalmol*, 156: 706-714, 2013.
102. van Dijk HW, Kok PH, Garvin M, *et al.*: Selective loss of inner retinal layer thickness in type 1 diabetic patients with minimal diabetic retinopathy. *Invest Ophthalmol Vis Sci*, 50: 3404-3409, 2009.
103. van Dijk HW, Verbraak FD, Kok PH, *et al.*: Early neurodegeneration in the retina of type 2 diabetic patients. *Invest Ophthalmol Vis Sci*, 53: 2715-2719, 2012.
104. De Clerck EE, Schouten JS, Berendschot TT, *et al.*: New ophthalmologic imaging techniques for detection and monitoring of neurodegenerative changes in diabetes: A systematic review. *Lancet Diabetes Endocrinol*, 3: 653-663, 2015.
105. Balendra SI, Normando EM, Bloom PA, Cordeiro MF: Advances in retinal ganglion cell imaging. *Eye (Lond)*, 29: 1260-1269, 2015.
106. Querques G, Lattanzio R, Querques L, *et al.*: Enhanced depth imaging optical coherence tomography in type 2 diabetes. *Invest Ophthalmol Vis Sci*, 53: 6017-6024, 2012.
107. Tavares Ferreira J, Vicente A, Proenca R, *et al.*: Choroidal thickness in diabetic patients without diabetic retinopathy. *Retina*, 38: 795-804, 2018.
108. Wang JC, Láíns I, Providência J, *et al.*: Diabetic choroidopathy: Choroidal vascular density and volume in diabetic retinopathy with swept-source optical coherence tomography. *Am J Ophthalmol*, 184: 75-83, 2017.
109. Thambyrajah J, Landray MJ, McGlynn FJ, *et al.*: Abnormalities of endothelial function in patients with predialysis renal failure. *Heart*, 83: 205-209, 2000.

110. Stehouwer CDA, Henry RMA, Dekker JM, *et al.*: Microalbuminuria is associated with impaired brachial artery, flow-mediated vasodilation in elderly individuals without and with diabetes: Further evidence for a link between microalbuminuria and endothelial dysfunction—the hoorn study. *Kidney Int*, 66: S42-S44, 2004.
111. Chua J, Chin CWL, Hong J, *et al.*: Impact of hypertension on retinal capillary microvasculature using optical coherence tomographic angiography. *J Hypertens*, 37: 572-580, 2019.
112. Burton JO, Jefferies HJ, Selby NM, McIntyre CW: Hemodialysis-induced repetitive myocardial injury results in global and segmental reduction in systolic cardiac function. *Clin J Am Soc Nephrol*, 4: 1925-1931, 2009.
113. Pahor D, Gracner B, Gracner T, Hojs R: Optical coherence tomography findings in hemodialysis patients. *Klin Monbl Augenheilkd*, 225: 713-717, 2008.
114. Shin YU, Lee SE, Kang MH, *et al.*: Evaluation of changes in choroidal thickness and the choroidal vascularity index after hemodialysis in patients with end-stage renal disease by using swept-source optical coherence tomography. *Medicine* 98: e15421, 2019.
115. Shin YU, Lee DE, Kang MH, *et al.*: Optical coherence tomography angiography analysis of changes in the retina and the choroid after haemodialysis. *Sci Rep*, 8: 17184, 2018.
116. Zhang Y, Weng H, Li Q, Wang Z: Changes in retina and choroid after haemodialysis assessed using optical coherence tomography angiography. *Clin Exp Optom*, 101: 674-679, 2018.
117. Chen H, Zhang X, Shen X: Ocular changes during hemodialysis in patients with end-stage renal disease. *BMC Ophthalmol*, 18: 208, 2018.
118. Chang IB, Lee JH, Kim JS: Changes in choroidal thickness in and outside the macula after hemodialysis in patients with end-stage renal disease. *Retina*, 37: 896-905, 2017.

119. Ishibazawa A, Nagaoka T, Minami Y, *et al.*: Choroidal thickness evaluation before and after hemodialysis in patients with and without diabetes. *Invest Ophthalmol Vis Sci*, 56: 6534-6541, 2015.
120. Jung JW, Chin HS, Lee DH, *et al.*: Changes in subfoveal choroidal thickness and choroidal extravascular density by spectral domain optical coherence tomography after haemodialysis: A pilot study. *Br J Ophthalmol*, 98: 207-212, 2014.
121. Yang SJ, Han YH, Song GI, *et al.*: Changes of choroidal thickness, intraocular pressure and other optical coherence tomographic parameters after haemodialysis. *Clin Exp Optom*, 96: 494-499, 2013.
122. Ulas F, Dogan U, Keles A, *et al.*: Evaluation of choroidal and retinal thickness measurements using optical coherence tomography in non-diabetic haemodialysis patients. *Int Ophthalmol*, 33: 533-539, 2013.
123. Jung JW, Yoon MH, Lee SW, Chin HS: Effect of hemodialysis (hd) on intraocular pressure, ocular surface, and macular change in patients with chronic renal failure. Effect of hemodialysis on the ophthalmologic findings. *Graefes Arch Clin Exp Ophthalmol*, 251: 153-162, 2013.
124. Theodossiadis PG, Theodoropoulou S, Neamonitou G, *et al.*: Hemodialysis-induced alterations in macular thickness measured by optical coherence tomography in diabetic patients with end-stage renal disease. *Ophthalmologica*, 227: 90-94, 2012.
125. Demir MN, Eksioglu U, Altay M, *et al.*: Retinal nerve fiber layer thickness in chronic renal failure without diabetes mellitus. *Eur J Ophthalmol*, 19: 1034-1038, 2009.
126. Cheung CY, Ikram MK, Chen C, Wong TY: Imaging retina to study dementia and stroke. *Prog Retin Eye Res*, 57: 89-107, 2017.

127. Findlay MD, Dawson J, Dickie DA, *et al.*: Investigating the relationship between cerebral blood flow and cognitive function in hemodialysis patients. *J Am Soc Nephrol*, 30: 147-158, 2019.
128. Berindan K, Nemes B, Szabo RP, Modis L, Jr.: Ophthalmic findings in patients after renal transplantation. *Transplant Proc*, 49: 1526-1529, 2017.
129. Altinkaynak H, Kara N, Sayın N, *et al.*: Subfoveal choroidal thickness in patients with chronic heart failure analyzed by spectral-domain optical coherence tomography. *Curr Eye Res*, 39: 1123-1128, 2014.
130. Ahmad M, Kaszubski PA, Cobbs L, *et al.*: Choroidal thickness in patients with coronary artery disease. *PLoS One*, 12: e0175691, 2017.
131. Wang J, Jiang J, Zhang Y, *et al.*: Retinal and choroidal vascular changes in coronary heart disease: An optical coherence tomography angiography study. *Biomed Opt Express*, 10: 1532-1544, 2019.
132. Arnould L, Seydou A, Gabrielle PH, *et al.*: Subfoveal choroidal thickness, cardiovascular history, and risk factors in the elderly: The montrachet study. *Invest Ophthalmol Vis Sci*, 60: 2431-2437, 2019.
133. Jia Y, Bailey ST, Wilson DJ, *et al.*: Quantitative optical coherence tomography angiography of choroidal neovascularization in age-related macular degeneration. *Ophthalmology*, 121: 1435-1444, 2014.
134. Hwang TS, Jia Y, Gao SS, *et al.*: Optical coherence tomography angiography features of diabetic retinopathy. *Retina*, 35: 2371-2376, 2015.
135. Vadala M, Castellucci M, Guarrasi G, *et al.*: Retinal and choroidal vasculature changes associated with chronic kidney disease. *Graefes Arch Clin Exp Ophthalmol*, 257: 1687-1698, 2019.

136. Sun Z, Tang F, Wong R, *et al.*: Oct angiography metrics predict progression of diabetic retinopathy and development of diabetic macular edema: A prospective study. *Ophthalmology*, 2019.
137. Kim K, Kim ES, Yu SY: Optical coherence tomography angiography analysis of foveal microvascular changes and inner retinal layer thinning in patients with diabetes. *Br J Ophthalmol*, 102: 1226-1231, 2018.
138. Sohn EH, van Dijk HW, Jiao C, *et al.*: Retinal neurodegeneration may precede microvascular changes characteristic of diabetic retinopathy in diabetes mellitus. *Proc Natl Acad Sci U S A*, 113: 2655-2664, 2016.
139. Alicic RZ, Rooney MT, Tuttle KR: Diabetic kidney disease: Challenges, progress, and possibilities. *Clin J Am Soc Nephrol*, 12: 2032-2045, 2017.
140. Cheung CY, Tang F, Ng DS, *et al.*: The relationship of quantitative retinal capillary network to kidney function in type 2 diabetes. *Am J Kidney Dis*, 71: 916-918, 2018.
141. Chawla LS, Amdur RL, Amodeo S, *et al.*: The severity of acute kidney injury predicts progression to chronic kidney disease. *Kidney Int*, 79: 1361-1369, 2011.
142. Odutayo A, Wong CX, Farkouh M, *et al.*: Aki and long-term risk for cardiovascular events and mortality. *J Am Soc Nephrol*, 28: 377, 2017.
143. Alan G, Guenancia C, Arnould L, *et al.*: Retinal vascular density as a novel biomarker of acute renal injury after acute coronary syndrome. *Sci Rep*, 9: 8060, 2019.
144. Arnould L, Guenancia C, Azemar A, *et al.*: The eye-mi pilot study: A prospective acute coronary syndrome cohort evaluated with retinal optical coherence tomography angiography. *Invest Ophthalmol Vis Sci*, 59: 4299-4306, 2018.
145. Martens RJH, Houben A, Kooman JP, *et al.*: Microvascular endothelial dysfunction is associated with albuminuria: The maastricht study. *J Hypertens*, 2018.

146. Sorensen BM, Houben AJ, Berendschot TT, *et al.*: Prediabetes and type 2 diabetes are associated with generalized microvascular dysfunction: The maastricht study. *Circulation*, 134: 1339-1352, 2016.
147. Delles C, Michelson G, Harazny J, *et al.*: Impaired endothelial function of the retinal vasculature in hypertensive patients. *Stroke*, 35: 1289-1293, 2004.
148. Bruckmann A, Seeliger C, Lehmann T, *et al.*: Altered retinal flicker response indicates microvascular dysfunction in women with preeclampsia. *Hypertension*, 66: 900-905, 2015.
149. Nägele MP, Barthelmes J, Ludovici V, *et al.*: Retinal microvascular dysfunction in hypercholesterolemia. *J Clin Lipidol*, 12: 1523-1531.e1522, 2018.
150. Nägele MP, Barthelmes J, Ludovici V, *et al.*: Retinal microvascular dysfunction in heart failure. *Eur Heart J*, 39: 47-56, 2018.
151. Zhi Z, Chao JR, Wietecha T, *et al.*: Noninvasive imaging of retinal morphology and microvasculature in obese mice using optical coherence tomography and optical microangiography. *Invest Ophthalmol Vis Sci*, 55: 1024-1030, 2014.
152. Patel PJ, Foster PJ, Grossi CM, *et al.*: Spectral-domain optical coherence tomography imaging in 67 321 adults: Associations with macular thickness in the uk biobank study. *Ophthalmology*, 123: 829-840, 2016.
153. McCormick E: Oct roll out in every specsavers announced <https://www.Aop.Org.Uk/ot/industry/high-street/2017/05/22/oct-rollout-in-every-specsavers-announced>: Accessed:20th July 2018
154. LeCun Y, Bengio Y, Hinton G: Deep learning. *Nature*, 521: 436-444, 2015.
155. Gulshan V, Peng L, Coram M, *et al.*: Development and validation of a deep learning algorithm for detection of diabetic retinopathy in retinal fundus photographs. *JAMA*, 316: 2402-2410, 2016.

156. Poplin R, Varadarajan AV, Blumer K, *et al.*: Prediction of cardiovascular risk factors from retinal fundus photographs via deep learning. *Nat Biomed Eng*, 2: 158-164, 2018.
157. De Fauw J, Ledsam JR, Romera-Paredes B, *et al.*: Clinically applicable deep learning for diagnosis and referral in retinal disease. *Nat Med*, 24: 1342-1350, 2018.
158. Giani A, Cigada M, Choudhry N, *et al.*: Reproducibility of retinal thickness measurements on normal and pathologic eyes by different optical coherence tomography instruments. *Am J Ophthalmol*, 150: 815-824, 2010.
159. Corvi F, Pellegrini M, Erba S, *et al.*: Reproducibility of vessel density, fractal dimension, and foveal avascular zone using 7 different optical coherence tomography angiography devices. *Am J Ophthalmol*, 186: 25-31, 2018.

Table legends**Table 1.** *Retinal vascular metrics from retinal photography***Table 2.** *Retinal vascular metrics to predict incident or progressive chronic kidney disease*

BP – blood pressure, AVR – arteriole-to-venule ratio, OR – odds ratio, CRAE – central retinal arteriolar equivalents, CRVE – central retinal venular equivalents, RR – risk ratio, IFG – impaired fasting glucose, HR – hazard ratio, eGFR – estimated glomerular filtration rate, CKD – chronic kidney disease, *Df* - fractal dimension, ESRD – end stage renal disease. All values are mean.

Table 3. *Chortioretinal layer metrics from optical coherence tomography*

Table 4. *Haemodialysis and OCT metrics.* Studies examining OCT metrics before and after a haemodialysis session in patients on long-term renal replacement therapy. ↑ denotes increase, ↓ denotes decrease. UF – achieved ultrafiltration volume, BP – blood pressure, IOP – intraocular pressure, RNFL – retinal nerve fibre layer, EDI – enhanced depth imaging, L – litres, SBP – systolic blood pressure, DBP – diastolic blood pressure. All values are mean.

Table 1.

Metric	Derivation	Interpretation	Strengths	Weaknesses
Central retinal arteriolar equivalents (CRAE)	Widths of reflective erythrocyte column within vessel lumen from six largest arterioles located in a zone 0.5-1 disc diameters from optic disc margin	Summarised surrogate measure of internal arteriolar widths that reflect narrowing or widening	Provides insight into disease affecting arterioles Relatively easy to obtain and automate	Summarised rather than absolute values Potential for magnification and positioning errors Values are not true vessel widths nor cross-sectional area which may be more relevant to disease
Central retinal venular equivalents (CRVE)	Widths of reflective erythrocyte column within vessel lumen from six largest venules located in a zone 0.5-1 disc diameters from optic disc margin	Summarised surrogate measure of internal venular width that reflect narrowing or widening	Provides insight into disease affecting venules Relatively easy to obtain and automate	Summarised rather than absolute values Potential for magnification and positioning errors Values not true vessel widths nor cross-sectional area which may be more relevant to disease
Arteriole-to-venule ratio (AVR)	Ratio of CRAE to CVRE	Changes usually indicative of generalised arteriolar narrowing	Avoids magnification errors Dimensionless	Provides little insight to underlying pathophysiology If used alone, can lead to incorrect inferences: both CRVE and CRAE narrow with increasing BP producing a normal AVR masking any association.
Fractal dimensions (D_f)	Images are binarised and vessel maps are broken up into short segments ('skeletonisation'). Entire image divided into boxes and those containing a vessel segment are counted. Process is repeated with different box sizes. The number of boxes with vessel segments is plotted against the total number of boxes in the image.	Index of vessel network spatial occupancy (complexity). Reduced (sparse) or increased (dense) complexity relative to health or within a cohort reflect suboptimal vascular network geometry.	Based on robust models of optimality of vascular branching May be more sensitive than calibres in reflecting microvascular disease in other organs beds	Less widely studied than calibres Simplifies 3-dimensional vascular networks into 2-dimensional skeletonised maps

Table 2.

Study	Country	n	Population Mean age	Retinal metric	Clinical outcome	Hypertension	Mean BP	Diabetes	Index serum creatinine or eGFR	Follow up	Results
Wong ⁵⁹ 2004 Prospective, Population - based cohort	US	10,056	White and African- American adults, eGFR >60mls/min 60 years	AVR	Incident renal dysfunction: rise in serum creatinine by ≥35μmol/L or hospital admission/death coded for renal disease	50%	127/70 mmHg	22%	80μmol/L	6 years	3% developed CKD Smallest AVR associated with greater change in serum creatinine (4 vs 2μmol/L)
Wong ⁶² 2004 Prospective, Population - based cohort	US	557	Type 1 diabetics eGFR >90mls/min, proteinuria <0.3g/L 31 years	CRAE CRVE	Incident renal insufficiency: eGFR <60mls/min Incident gross proteinuria: >0.3g/L	No data	120/76 mmHg	100%	No data	16 years	20% developed CKD 33% developed proteinuria Widest CRVE quartile associated with increased incidence of CKD and proteinuria CKD: adjusted RR 1.5(1.05-2.2) Proteinuria: adjusted RR 1.5(1.2-2) No association for CRAE
Edwards ⁶³ 2004 Prospective, Population - based cohort	US	1,394	Adults aged >65 years 78 years	AVR	Change in serum creatinine Decline in renal function: increase in serum creatinine by ≥27μmol/L and fall in eGFR by ≥20%	57%	131/67 mmHg	17%	89μmol/L 70mls/min	4 years	4-5% developed a significant increase in serum creatine or fall in eGFR AVR showed no associations with changes in renal function Retinopathy associated with greater risk of decline in renal function: Adjusted OR 2.8-3.2 vs. no retinopathy
Sabanayagam ⁶⁴ 2011 Prospective, Population - based cohort	US	3,199	White adults with eGFR >60mls/min 59 years	CRAE CRVE	Incident CKD: eGFR <60mls/min and ≥5% decrease from baseline	45%	130/78 mmHg	9%	85mls/min	15 years	5% developed CKD No association CRAE or CRVE with incident CKD No association with eGFR and incident CRAE narrowing or CRVE widening
Yau ⁶⁵ 2011	US	4,594	Multi-ethnic adults, eGFR	CRAE CRVE	Incident CKD: eGFR <60mls/min	40%	127/71 mmHg	11%	76mls/min	4.8 years	5% developed CKD

Prospective, Population - based cohort			>60mls/min 64 years									Narrowest CRAE tertile associated with incident CKD in white patients only : adjusted HR 1.78 (1.01-3.1) vs. widest; increased to 2.95 when analysing those without hypertension or diabetes
												No association with CRVE
Baumann ⁶⁶ 2014 Prospective	Germany	141	Adults, CKD stage 2-4 61 years	CRAE	Progression of CKD: 50% decline in eGFR or start of RRT	No data	137/76 mmHg	46%	48mls/min	3.9 years	17% had progression in CKD Narrowest CRAE tertile associated with progression in CKD: adjusted OR 3 (1.2-7.5) vs. widest CRAE Narrowest CRAE in presence of albuminuria associated with 10-fold increased risk of CKD progression, compared to 3-fold risk seen with narrow CRAE or albuminuria alone	
Grunwald ⁶⁷ 2014 Prospective, Population - based cohort	US	1852	Adults, eGFR 20-70mls/min 62 years	AVR CRAE CRVE	Progression in CKD: ESRD/RRT, Change in eGFR slope	90%	130/80 mmHg	47%	40mls/min	2.3 years	8% developed ESRD eGFR decline 0.53ml/min Greater AVR associated with ESRD and steeper eGFR decline: adjusted HR 3.1 (1.5-6.4). No associations with CRAE and CRVE	
Yip ⁶⁸ 2015 Prospective, Population - based cohort	Singapore	5763	Malay adults 55 years	AVR CRAE CRVE <i>Df</i>	Incident ESRD: defined by start of renal replacement therapy	55%	140/70 mmHg	34%	77mls/min	4.3 years	0.4% developed ESRD No associations for vascular metrics and risk of ESRD in adjusted analyses Retinopathy predicted ESRD.	
Yip ⁶⁹ 2017 Prospective, Population - based cohort	Singapore	1256	Malay adults 56 years	CRAE CRVE Tortuosity <i>Df</i> Branching angles	Incident CKD: eGFR <60mls/min	58%	150/80 mmHg	25%	80mls/min	6 years	6% developed incident CKD Narrower CRAE associated with incident CKD: adjusted HR 1.3 (1-1.78) as continuous variable. Widest CRVE tertile associated with incident CKD: adjusted HR 2.4 (1.1-5.9) vs. narrowest No other vascular metrics associated with incident CKD	

McKay ⁷⁰ 2018	Scotland	1068	Adults eGFR ≥60mls/min	CRAE CRVE Tortuosity <i>Df</i> Branching angles	Change in eGFR: 'Progressors': eGFR <60mls or ≥15% decline 'Non-progressors': <10% decline	No data	138/77 mmHg	100%	94mls/min	3 years	31% had 'progressive' CKD No baseline retinal metric predicted progression of CKD in unadjusted or adjusted analyses.
Prospective, Population - based cohort			63 years								

Table 3.

Metric	Derivation	Interpretation	Strengths	Weaknesses
Retinal thickness	<p>Calculated from the number of A-scan pixels between the internal limiting and Bruch's membranes.</p> <p>Sequential A-scans in horizontal or vertical plane generate a two-dimensional thickness profile across the retina, the B-scan</p>	<p>Average thickness of peripheral and central retinal subfields</p> <p>Thinning predominantly reflects neuronal loss. May also reflect intra-retinal capillary rarefaction</p> <p>Thickening reflects accumulation of oedema, vascular exudates or cellular debris</p>	<p>Can allow detection of differential patterns of retinopathy: global thinning vs. predominantly central or peripheral subfield thinning</p> <p>Easy to obtain, automated and highly reproducible</p> <p>Segmentation of retinal sublayers can provide novel insight into pathogenesis such as ganglion cell layer</p>	<p>Layer and subfield boundaries not standardised across devices</p> <p>Overall thickness may miss sublayer thinning or thickening</p> <p>Cannot differentiate between neuronal or vascular structures</p>
Macular volume	<p>Calculated as product of retinal thickness and scan area. The scan area can be subdivided into the Early Treatment of Retinopathy in Diabetes Study (ETDRS) map of 6mm, 3mm and 1mm concentric rings centred on the fovea, producing 9 subfields</p>	<p>Global and regional volumes of key region for vision</p> <p>Thinning predominantly reflects neuronal loss. May also reflect intra-retinal capillary rarefaction.</p> <p>Thickening reflects accumulation of oedema, vascular exudates or cellular debris</p>	<p>Can allow early detection and tracking of differential patterns of maculopathy</p> <p>Segmentation of sublayers can provide novel insight into pathogenesis</p> <p>Easy to obtain, automated and highly reproducible</p>	<p>Accuracy dependent on total number of stacked horizontal B-scans within scan area</p> <p>Layer boundaries and B-scan protocols not standardised across devices</p>
Retinal nerve fibre layer thickness	<p>Calculated from the number of A-scan pixels between the internal limiting membrane and ganglion cell layer</p> <p>Sequential A-scans in horizontal, vertical plane or circular plane centred on the optic disc generate a thickness profile</p>	<p>Global and regional assessment of ganglion cell (GC) axon number</p> <p>Thinning reflects GC axonal loss</p> <p>Thickening reflects axonal oedema seen in inflammation, ischaemia or intracranial hypertension</p>	<p>Specific biomarker of optic neuropathy and wider central neurological disease</p> <p>Allows earlier detection and tracking of differential patterns of neuropathy.</p> <p>Easy to obtain, automated and highly reproducible</p> <p>Standardized normative range available for glaucoma and neurological disease</p>	<p>Blood vessels (and glial cells) within RNFL are included in measurement so not truly representative of GC axon population</p> <p>Segmentation errors can occur</p> <p>Susceptible to confounding by optical biometrics such as axial length, disc size, disc-fovea angle</p>
Choroidal thickness	<p>No precise definition or standard methodology. Calculated from the number of A-scan pixels from Bruch's membrane to choroidoscleral interface.</p> <p>Often manually measured at several discrete locations</p> <p>Newer devices provide automatic segmentation to automatically calculate regional choroidal thickness and volume in a manner similar to that for retinal thickness and volume.</p>	<p>Coarse measure of a dense vascular layer containing arterioles, capillaries, venules and veins.</p> <p>Thinning reflects vascular changes including reduced blood flow, vasoconstriction or rarefaction. Contribution of non-vascular components unclear.</p> <p>Thickening may due to increased blood flow, vasodilatation or oedema. Contribution of non-vascular components unclear.</p>	<p>Easy to obtain, increasingly automated and reproducible</p> <p>Assess critical vascular supply to retina and reveals new insight into macular disease</p>	<p>Inaccessible location continues to limit comprehensive vascular assessment</p> <p>Does not differentiate between vascular and non-vascular structures</p> <p>Susceptible to confounding by optical biometrics such as axial length</p> <p>No standardized normative range</p>

Author	Year	Country	Device	<i>n</i>	Age	Proportion with diabetes	Dialysis vintage	UF volume	Δ weight	Δ BP	Δ IOP	Δ retinal thickness	Δ choroidal thickness	Δ RNFL	Δ vessel density
--------	------	---------	--------	----------	-----	-----------------------------	---------------------	--------------	----------	------	-------	------------------------	--------------------------	--------	---------------------

Table 4.

Shin ¹¹⁴	2019	South Korea	DRI Triton	32	56 years	~66%	6 years	3L	↓ 2.6kg	↓ SBP ~12mmHg	No change	-	↓ ~5%	-	-
Shin ¹¹⁵	2018	South Korea	DRI OCT1 Atlantis	29	56 years	~52%	5.8 years	3L	↓ 2.7g	↓ SBP ~10mmHg	No change	No change	↓ ~7%	-	↓ ~3%
Zhang ¹¹⁶	2018	China	AngioVue	77	53 years	~50%	4.5 years	2.5L	-	↓ SBP ~7mmHg	No change	↓ ~2%	No change	-	↓ ~3%
Chen ¹¹⁷	2018	China	Cirrus HD	90	58 years	~13%	5.8 years	-	-	↓ SBP ~10mmHg ↓ DBP ~7mmHg	No change	No change	↓ ~12%	↑ ~3%	-
Chang ¹¹⁸	2017	South Korea	Spectralis with EDI	54	60 years	~60%	5 years	-	↓ 2.3kg	↓ SBP ~15mmHg ↓ DBP ~4mmHg	↓ ~10%	-	↓ ~10%	No change	-
Ishibazawa ¹¹⁹	2015	Japan	RetinaScan No EDI	77	67 years	~50%	4.7 years	2.5L	↓ 2.2kg	↓ SBP ~14mmHg ↓ DBP ~4mmHg	No change	No change	↓ ~10%	-	-
Jung ¹²⁰	2014	South Korea	Spectralis No EDI	19	51 years	~50%	3.5 years	-	↓ 2.1kg	↓ SBP ~16mmHg	No change	-	↑ ~5%	-	-
Yang ¹²¹	2013	South Korea	Spectralis with EDI	34	58 years	~25%	6 years	-	↓ 2.8 kg	No change	↓ ~10%	No change	↓ ~6%	No change	-
Ulas ¹²²	2013	Turkey	Spectralis with EDI	21	61 years	-	2.4 years	3L	-	No change	No change	No change	↓ ~10%	-	-
Jung ¹²³	2013	South Korea	Spectralis No EDI	30	54 years	~40%	4.3 years	-	↓ 1.9kg	↓ SBP ~17mmHg ↓ DBP ~7mmHg	↓ ~15%	↓ ~2%	-	-	-
Theodosiadis ¹²⁴	2011	Greece	OCT3 Stratus	72	62 years	100%	2.8 years	-	↓ 2.5kg	No change	-	↓ ~4%	-	-	-
Demir ¹²⁵	2008	Turkey	OCT3 Stratus	36	41 years	-	3.5 years	-	-	-	-	-	-	No change	-

Figure legends

Figure 1. *Initiation and consequences of microvascular disease.*⁵

Light blue arrows show additional association/contribution between insults. *Dark blue arrows* indicate sequence of events leading to development and progression of end-organ dysfunction. GFR: glomerular filtration rate; SVD: small vessel disease; CAD: coronary artery disease; LVH: left ventricular hypertrophy.

Figure 2. *The eye as a window to the kidney*

The microcirculation of the eye is characterised by multiple capillary networks which, although arranged in close proximity, have striking structural and functional differences. This is also true of the renal microcirculation.

A. Upper panel – cross-sectional diagram of glomerular capillary

Lower panel – cortico-medullary microcirculation organisation, oxygen gradients and actions of renal-angiotensin-aldosterone and endothelin systems

B. Upper panel – cross-sectional diagram of choroidal capillary

Lower panel – chorioretinal microcirculation organisation, oxygen gradients and actions of renal-angiotensin-aldosterone and endothelin systems

pO₂ – partial pressure of oxygen; ON – optic nerve; RNFL – retinal nerve fibre layer; CRA – central retinal artery; CRV – central retinal vein; RAAS – renin-angiotensin-aldosterone system; ET – endothelin system; AT₁R – angiotensin II type 1 receptors; ET_AR – endothelin type A receptor; ET_BR – endothelin type B receptor.

Figure 3. *Retinal vascular network geometric indices*

Retinal photographs (left panels) of the left eye using Canon CR-1 fundus camera with a field of view of 45° from a healthy volunteer (**A**) and patient with CKD (**B**). Arterial and venous

branches are binarised and segmented (middle panels) before being transformed into vessel (arterial) skeleton maps (right panels) for fractal dimension (Df) analyses. The vessel segmentation and skeleton maps demonstrate retinal vessel rarefaction in CKD compared to health that is not evident from the standard retinal photographs; health $Df_{arteries} = 1.47$; CKD $Df_{arteries} = 1.18$. Retinal photographs and segmentation images used under Creative Commons licence from <https://www5.cs.fau.de/research/data/fundus-images/>. Vessel skeleton map images kindly provided by Stephen Hogg (VAMPIRE[®] group, University of Dundee, United Kingdom).

Figure 4. Deep imaging with OCT

Right eye *en-face* confocal scanning laser ophthalmoscope (CLSO, left panels) and OCT (right panels) images using the Heidelberg SPECTRALIS[®] Spectral-Domain OCT machine (SD-OCT, Heidelberg Engineering, Heidelberg, Germany). in health (**A**, **B** & **C**) and CKD (**D**) with enhanced depth imaging (**C** & **D**) Scale bars: 200 μ m.

A. SD-OCT enables the identification of specific cell layers within the retina in high resolution. *Left panel* shows an *en face* CLSO image centred over the macula. Green line represents level and direction of cross section of corresponding OCT image running from left to right. *Right panel* is an OCT image demonstrating individual layers within the retina. Retinal thickness is defined as the area bounded by internal limiting membrane (ILM) and Bruch's membrane (BM).

B. *Left panel* is a CLSO image centred over the optic nerve head with line of cross-section (green) circled around the peri-papillary region. The dark blue line defines the distance from optic disc to fovea. *Right panel* is an OCT image demonstrating retinal thickness from the circular cross-section around the optic nerve head in the left image. The green line running

from left to right corresponds to the direction of cross-section of the green circle in left panel. Retinal nerve fibre layer thickness as defined as the area bordered by red and cyan lines.

C. CSLO (*left panel*) and OCT with Enhanced Depth Imaging (EDI, *right panel*) in a **healthy subject**. EDI enables identification of deeper structures including the highly vascularised choroid. We measure choroidal thickness at 3 locations: I = 2 mm nasal to the fovea, II = subfoveal, III = 2 mm temporal to the fovea. The corresponding locations on the macula are indicated by yellow arrows.

D. CLSO (*left panel*) and OCT with EDI (*right panel*) in an age-, sex-matched **subject with CKD** demonstrating comparative thinning of the choroid at all 3 locations. The corresponding locations on the macula are indicated by yellow arrows.

Figure 5. OCT angiography in health and chronic kidney disease

Right eye *en face* OCT angiograms centred on the macula using the AngioVue[®] Imaging System (Optovue, Inc., Freemont, California) in a healthy volunteer (**A**) and an age- and sex-matched patient with proteinuric chronic kidney disease (CKD, **B**).

Left and middle panels: Peri-macular superficial and deep capillary plexuses with the foveal avascular zone (FAZ) represented by central black circular region. Compared to health, a wider FAZ and a disorganised branching pattern are evident in the CKD patient and are suggestive of rarefaction and microvascular damage.

Right panels: Peri-macular superficial retinal vessels and the foveal avascular zone with colour map overlays of software-calculated vessel density. Red denotes high vessel density; green denotes moderate vessel density; blue/navy denotes low vessel density. There is fewer

regions with high / moderate vessel density (red/green regions) CKD compared to health.

Note these images are not from the same subjects as the left and middle panels.

Journal Pre-proof

Supplementary material**Supplementary figure legends****Supplementary figure 1. *Alport syndrome-associated retinopathy.***

Ultra-wide field scanning laser ophthalmoscope photograph of left eye from a male patient with end-stage renal disease secondary to X-linked Alport syndrome. The characteristic dot-and-fleck retinopathy is evident as green peri-macular deposits in the centre of the image. There is also associated loss of foveal reflex due to macular thinning. The presence of Alport-associated retinopathy can help diagnosis, suggest inheritance patterns, identify those at risk of progressive CKD and differentiate from mimics such as thin GBM disease which has no associated retinal features.^{14, 15}

Supplementary figure 2. *Retinal photography and fundus retinal calibre assessment*

A. Right eye digital retinal photograph using Canon CR-1 fundus camera with a field of view of 45°.

B. Right eye scanning laser ophthalmoscope image centred over optic disc using the Heidelberg SPECTRALIS® Spectral-Domain OCT machine (SD-OCT, Heidelberg Engineering, Heidelberg, Germany). The centre of the optic disc is manually determined. A standard set of concentric circular measurement zones commonly used in the analysis of fundus camera images is mapped from this point as shown. Zone 'A' is the area 0.5 to 1 optic disc diameters away from the centre as bounded by the white dotted lines. The vessel analysis software VAMPIRE® (University of Dundee, United Kingdom) selects the six widest arterioles (red) and venules (blue) crossing zone A to calculate CRAE, CRVE and AVR.

Supplementary figure 3. *Retinal optical coherence tomography.*

Blue lines represent fibre paths. *Red lines* represent optical paths. *Green lines* represent signal paths. Low coherence light (typically ~800 nm wavelength) is split into a sample beam and reference beam. The sample beam is shone onto the retina and reflected back as ‘light echoes’. The reference beam is directed to a mirror positioned at a known distance from the light source. A range of ‘sample’ light echoes each return at different times depending on the distance of the reflecting tissue from the light source. Returning ‘sample’ and ‘reference’ light echoes are re-united and directed to a photodetector. An interference signal is detected when the time delays between the ‘sample’ and ‘reference’ light echoes is small, *i.e.* the distance of reference mirror matches the distance of the reflecting tissue. Moving the reference mirror (positions A to C) alters the distance the reference beam/echo must travel and thus changes the time delay between reference and sample echoes. At each new reference mirror distance, the reference echo time delay will closely match a different sample echo time delay, generating a new interference signal corresponding to a deeper/shallower reflecting tissue layer. Sequential movement of reference mirror allows the construction of a single interference depth profile: the A-scan. A-scans obtain depth profiles along the z-axis. The lateral scanning mirror is rotated through positions 1 to 4 along the x-axis to obtain sequential adjacent A-scans which are used to generate a single horizontal B-scan. The vertical scanning mirror is elevated/lowered along the y-axis to obtain horizontal B-scans at multiple levels. B-scans can then be stacked to create a volume scan (**Supplementary videos 1 and 2**).

Supplementary figure 4. Retinal layer segmentation by OCT. Close up of horizontal line OCT scan through the macula of the right eye with automated segmentation of individual retinal layers. RNFL – retinal nerve fibre layer, GCL – ganglion cell layer, IPL – inner plexiform layer, INL – inner nuclear layer, OPL – outer plexiform layer, ONL – outer nuclear

layer, PR – photoreceptor layer, RPE – retinal pigment epithelium, BM – Bruch’s membrane, CH – choroid.

Supplementary figure 5. OCT angiography

Right eye 3 x 3mm OCT angiograms *en face* (left panels) and in cross-section (right panels), centred on the macula, using the AngioVue® Imaging System (Optovue, Inc., Freemont, California).

A. Left panel: The peri-macular superficial capillary plexus and the foveal avascular zone.

Right panel: OCT image showing the level and boundaries of retinal layer segmentation the corresponds to *en face* angiogram. Red and green lines define the upper and lower limits respectively, of the segmentation band.

B. Left panel: The peri-macular deep capillary plexus and the foveal avascular zone. **Right**

panel: OCT image showing the level and boundaries of deeper retinal layer segmentation the corresponds to *en face* angiogram. Red and green lines define the upper and lower limits respectively, of the segmentation band.

C. Left panel: The outer (deepest) retinal layers are relatively avascular as shown and is thus

dependent on passive oxygenation from the deeper choroidal circulation. **Right panel:** OCT image showing the level and boundaries of outer retinal layer segmentation the corresponds to *en face* angiogram. Red lines define the upper and lower limits of the segmentation band.

D. Left panel: The subfoveal choriocapillaris is a dense mesh of capillaries underneath the pigment epithelium. Despite advances in OCT-A, imaging discrete vessels here remains

challenging. **Right panel:** OCT image showing the level and boundaries of choriocapillaris

segmentation the corresponds to *en face* angiogram. Red and green lines define the upper and lower limits respectively, of the segmentation band.

Supplementary video legends**Supplementary video 1. *OCT in health***

Video of a 3-dimensional rendered macular volume OCT scan of right eye from a healthy volunteer.

Supplementary video 2. *OCT in CKD*

Video of a 3-dimensional rendered macular volume OCT scan of right eye from an age- and sex-matched subject with CKD. Note marked thinning of choroidal vascular lying underneath the retina.

Supplementary video 3. *OCT angiography of macula in health*

Video of sequential 'layer by layer' OCT angiograms centred on macula of right eye from a healthy volunteer. The track bar on the left-hand side relates colour-coded anatomic localisation of retinal regions that correspond to the angiograms shown in main panel.

Supplementary video 4. *OCT angiography of optic disc in health*

Video of sequential 'layer by layer' OCT angiograms centred on fundus of right eye from a healthy volunteer. The track bar on the left-hand side relates colour-coded anatomic localisation of retinal regions that correspond to the angiograms shown in main panel.

Supplementary information is available on Kidney International's web site

