Hypertensive eye disease

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Competing interests

V.B. is consultant for GenSight Biologics and Neurophoenix. P.A.K. has acted as a consultant for Apellis, Bitfount, DeepMind, Roche and Novartis and is an equity owner in Big Picture Medical. P.A.K has received speaker fees from Allergen, Bayer, Heidelberg Engineering and Topcon. T.Y.W. is a consultant for Allergan, Bayer, Boehringer-Ingelheim, Eden Ophthalmic, Genentech, Iveric Bio, Merck, Novartis, Oxurion (ThromboGenics), Roche, Samsung, Shanghai Henlius and Zhaoke Pharmaceutical. T.Y.W. is an inventor, holds patents and is a co-founder of start-up companies (plano and EyRiS), which have interests in, and develop digital solutions for eye diseases.

Abstract

Hypertensive eye disease includes a spectrum of pathological changes, the most well-known being hypertensive retinopathy. Other commonly involved parts of the eye in hypertension include the choroid and optic nerve, sometimes referred to as hypertensive choroidopathy and hypertensive optic neuropathy. Together, hypertensive eye disease develops in response to acute and/or chronic elevation of blood pressure. Major advances in research over the past three decades have greatly enhanced our understanding of the epidemiology, systemic associations and clinical implications of hypertensive eye disease, particularly hypertensive retinopathy. Traditionally diagnosed via a clinical funduscopic examination, but increasingly documented on digital retinal fundus photographs, hypertensive retinopathy has long been considered a marker of systemic target organ damage (e.g., kidney disease) elsewhere in the body. Epidemiological studies indicate that hypertensive retinopathy signs are commonly seen in the general adult population, are associated with subclinical measures of vascular disease and predict risk of incident clinical cardiovascular events. New technologies, including development of non-invasive optical coherence tomography angiography, artificial intelligence (AI), and mobile ocular imaging instruments, have allowed further assessment and understanding of the ocular manifestations of hypertension and increase the potential that ocular imaging could be used for hypertension management and cardiovascular risk stratification.

1. Introduction

Hypertension, the leading risk factor for cardiovascular disease (CVD) and mortality worldwide,[1,2] has profound effects on both the structure and function of the eye.[3] Hypertensive eye disease includes a broad spectrum of pathological changes, the most well-known being hypertensive retinopathy. Other commonly involved parts of the eye in hypertension include the choroid and optic nerve, sometimes referred to as hypertensive choroidopathy and hypertensive optic neuropathy. Together, hypertensive retinopathy, choroidopathy and optic neuropathy develop in response to acute and/or chronic elevation of blood pressure (BP).[4] In addition to these primary effects of BP on the eye, hypertension is also a risk factor for many common eye conditions, such as diabetic retinopathy,[5] retinal vein occlusion,[6] retinal artery occlusion,[7] retinal artery emboli,[8] retinal arterial macroaneurysm,[9] and possibly age-related macular degeneration and glaucoma.[3,10-12] These eye conditions are not typically considered part of hypertensive eye disease and thus will not be discussed in this paper.

Because vascular remodelling in hypertension is the earliest and most common evidence of target organ damage (TOD),[13] hypertensive retinopathy with its typical arteriolar wall signs is also one of the most common and early manifestations of hypertension. How does elevated BP affect the vasculature and consequently, directly or indirectly the eye? There have been significant advances in our understanding of the role of the macrovasculature (large conduit arteries) and the microvasculature (small vessels) that participate in inter-linked processes leading to elevation of BP.[14-17] Elevation of BP is triggered by complex mechanisms involving the sympathetic nervous system, inflammation and activation of innate and adaptive immunity, the renin-angiotensin-aldosterone system and the endothelin system, as well as elevation of circulating and tissue adenosine triphosphate, endoperoxides and thromboxanes, and other mediators, including short chain fatty acids originating in gut microbiome dysbiosis. Higher BP contributes through the effects of increased pulsatility to conduit elastic or large vessel stiffening that then exaggerates the pulsatility.[18] Increased pulsatility that can already be present in younger hypertensive subjects penetrates deeply into the microcirculation, including the retinal vessels, inducing injury that leads to remodeling and endothelial dysfunction. Stiffening of the aorta and other elastic vessels progresses after middle age and accordingly in the elderly, pulse pressure widens progressively. As smaller vessels

are injured by BP pulsatility, tissue nutrient and gas exchange are impaired, and thus TOD occurs in the heart, kidneys, brain, and the eyes. In younger individuals genetically predisposed to high BP, increased salt intake or other exogenous or endogenous risk factors for hypertension including overweight and excess alcohol intake lead to enhanced sympathetic activity and vasoconstriction.[19] In obese individuals, loss of perivascular anticontractile factors plays a role in microvessel remodeling as well.[20] Enhanced vasoconstrictor responses and myogenic tone become embedded in an increased extracellular matrix, which results in the remodeling of small arteries and arterioles with subsequent narrowing of the lumen and increased media/lumen ratio, which manifest in the arterioles as narrowing and other arteriolar wall signs, which are described below. Exaggerated myogenic tone leads to closure of terminal arterioles, collapse of capillaries and venules, and functional rarefaction, eventually leading to anatomical rarefaction, which compromises tissue perfusion. The remodeling of the microcirculation raises resistance to flow, and accordingly BP, in a feedback process that over years results in stiffening of conduit arteries and systo-diastolic or predominantly systolic hypertension, and more rarely, predominantly diastolic hypertension. Thus, at different stages of life and the evolution of hypertension, the macro- and micro-circulation interact to contribute to BP elevation.[19,21] The eye is accordingly affected, with vascular injury manifesting as hypertensive retinopathy, choroidopathy and optic neuropathy, with its characteristic evolution described later in this article. **Figure 1** recapitulates the effect of elevated BP on the eye.

In parallel with research on pathogenesis and TOD effects of hypertension, there are also advances in our understanding of the epidemiology, systemic associations and thus clinical implications of hypertensive eye disease, particularly hypertensive retinopathy. Traditionally diagnosed via clinical funduscopic examination, hypertensive retinopathy signs are now more objectively and reliably documented on digital retinal fundus photographs. Signs of hypertensive retinopathy can broadly be grouped as retinal arteriolar wall changes (e.g., generalized and focal areas of arteriolar narrowing, arterio-venous crossing changes or nicking (AVN), sclerosis and opacification of the arteriolar wall, **Figure 2**) and retinal microvascular lesions that reflect more advanced tissue damage with a breakdown in blood-retina-barrier (e.g., dot, blot and flame-shaped haemorrhages and microaneurysms (HMA), hard exudates and cotton wool spots,

Figure 3). These signs reflect both the duration and severity of BP elevation. Arteriolar wall changes are typically seen in patients with mildly elevated BP over many years and are thus sometimes referred to as "mild" hypertensive retinopathy, while retinal microvascular lesions may be seen in patients with a shorter history of hypertension but with higher levels of BP, and therefore referred to as "moderate" hypertensive retinopathy.[22] However, the value of this somewhat arbitrary segregation of mild and moderate hypertensive retinopathy has been debated; for example, "mild" arteriolar changes have also been associated with significant TOD and CVD risk.[22,23] What is clear and more consistently demonstrated is that as a group, hypertensive retinopathy signs are common; large, population-based studies have shown evidence of both arteriolar and microvascular lesions on fundus photographs in 4% to 18.7% of the general non-diabetic adult population.[24-40] Finally, more severe and acute elevations of BP may result in a less commonly seen but specific form of acute retinopathy commonly referred to as "malignant" hypertensive retinopathy (**Figure 4**), which represents a medical emergency.[41]

Hypertensive retinopathy has long been considered a marker of systemic TOD elsewhere in the body.[42,43] While the relationship of retinal arteriolar changes with TOD is less consistently observed, retinal microvascular lesions have a stronger and more consistent association with other TOD of hypertension, subclinical vascular diseases, and future risk of clinical CVD events such as stroke, coronary artery disease, renal impairment, and cardiovascular mortality (details in the following sections). Thus, retinal evaluation, whether clinically or from fundus photographs, in patients with hypertension remains relevant for risk stratification and for tailoring treatment decisions. For example, international guidelines such as the 2018 European Society of Cardiology (ESC)/European Society of Hypertension (ESH) Guidelines for the management of hypertension continue to emphasize that a retinal evaluation is a basic examination for assessment of CVD risk and thus treatment initiation and BP targets.[44]

However, important questions remain to be answered regarding underlying mechanisms and clinical implications of hypertensive eye disease. The recent convergence of multiple technologies presents several opportunities. The development of new ophthalmic imaging instruments, such as optical coherence tomography (OCT) and OCT-angiography (OCT-A), which can non-invasively and rapidly image the thickness

of different layers of the retina, as well as retinal and choroidal microcirculation, and adaptive optics, which may allow non-invasive direct cellular-level visualization of damage, neurovascular coupling and inflammatory processes, provides unique opportunities for understanding the early pathophysiology of hypertensive TOD that can only be seen in the eye. In parallel, advances in the development of computing algorithms, AI and deep learning (DL) enhance analytic and predictive capabilities of retinal fundus images.[45,46] Lastly, innovations in mobile technology (e.g., small tabletop, handheld and smartphone retinal fundus cameras) and telemedicine platforms (e.g., 5G networks and cloud-based IT infrastructure) allow retinal images to be captured, stored, and examined outside of specialized research and hospital settings. Convergence of such technologies increases the potential that for retinal evaluations to be more easily integrated into future clinical pathways in the management of hypertension, as recommended in guidelines.[44]

This Primer discusses the epidemiology, pathophysiology, diagnosis, screening and prevention, and management strategies of hypertensive eye disease, with a focus on hypertensive retinopathy. Future trends for research and priorities in the next 5 to 10 years are also discussed. Recognizing the ocular effects of BP may allow healthcare providers to better manage patients with hypertension.

2. Epidemiology

2.1 Historical Perspective

In 1890s, Gunn was the first to describe the classic signs of hypertensive retinopathy and optic neuropathy in a case series of patients with hypertension and kidney disease which included generalized and focal arteriolar narrowing, AVN, flame- and blot-shaped retinal haemorrhages, cotton-wool spots, and swelling of the optic disk.[47,48] In a landmark study in 1939, Keith, Wagner and Barker showed that these signs were correlated with mortality in patients with untreated hypertension[49]. They categorized these retinal signs into a four-grade classification system, along with other markers of TOD, giving rise to the eponymous Keith-Wagner-Barker classification of hypertensive retinopathy.[49] Although widely used, this four-grade classification has been the subject of criticism because of the difficultly in distinguishing early features (grade 1 from 2).[42,50] Others (e.g., Wong-Mitchell) have thus proposed simplifying the classification

of hypertensive retinopathy into three grades, using more contemporary data on CVD risk based on population studies with retinal fundus photographs. The simplified three-grade Wong-Mitchell classification has higher intra-observer and interobserver level of agreement than the Keith-Wagner-Barker classification[23,50,51] although not yet fully tested and validated in large prospective studies. **Table 1** summarized the features of both classification systems.

It is noteworthy that malignant hypertension was diagnosed in the past with the presence of grade 3 or 4 hypertensive retinopathy, according to the Keith-Wagener-Barker classification. However, malignant hypertension has been recently reconceptualised to emphasis multi-organ damage, including kidney, heart, brain and microangiography.[41,52]

2.2 Prevalence

Over the past 30 years, large population-based studies have used retinal fundus photography and standardised assessment methods to document hypertensive retinopathy signs. These studies have clarified the prevalence of hypertensive retinopathy in the general non-diabetic adult population (40 years and older) across diverse racial/ethnic groups in different countries, with prevalence rates ranging from 4.0% to 18.7%.[24-40,53-56] In one of the first large studies, Klein et al reported the prevalence of hypertensive retinopathy in the population-based Beaver Dam Eye Study in the U.S.,[24] with rates of 13.5%, 3.3% and 7.8% for focal retinal arteriolar narrowing, AVN and HMA, respectively, among nondiabetic participants.[24] They reported that these signs were more frequent in older subjects and in subjects with hypertension, particularly among participants whose BP was elevated at the time of the examination, despite use of antihypertensive medications (i.e. referred to as uncontrolled hypertension in their study) than those whose BP was within normal limits while on antihypertensive medications (referred to as controlled hypertension).[24] This suggests that a retinal evaluation may provide an estimate of the level of BP in patients with hypertension (similar to the level of haemoglobin A_{1c} (HbA_{1c}) reflecting the overall glucose level in a diabetic patient).

Subsequently, similar findings have been reported in different populations.[25-27,31,54] In addition to elevated BP, various risk factors associated with hypertensive retinopathy

signs include a history of CVD and carotid artery thickening,[32,37,39,53] as well as smoking, dyslipidaemia, obesity, hyperglycaemia and impaired glucose tolerance, elevated creatinine levels and microalbuminuria.[29,33-37,39,55,56] Whereas inflammation has been shown to play a key role in hypertension pathophysiology, in the Multi-Ethnic Study of Atherosclerosis (MESA), a range of serum inflammatory factors were not found to be consistently associated with hypertensive retinopathy.[37]

Similar to the epidemiology of hypertension itself, hypertensive retinopathy may also vary by race/ethnicity (e.g., higher prevalence in Chinese,[37] African-Americans[30] and Afro-Caribbean,[57] than Caucasians) and possibly by gender (higher prevalence in men [34,36,39]). Observed demographic variation across studies may be attributable to methodological differences (e.g., variation in number of retinal fundus photographs taken between studies),[40] or reflect differences in hypertension control. For example, in the Atherosclerosis Risk in Communities (ARIC) study, severity of hypertension explained almost half of the excess prevalence of retinopathy in African-Americans compared with Caucasians.[30]

In contrast to focal arteriolar narrowing, AVN and retinal HMA, there are few epidemiological studies on generalized arteriolar narrowing, largely because this feature is not easily defined on retinal fundus photograph. In an effort to document the degree of generalized retinal arteriolar narrowing, computer softwares were developed to automatically measure retinal vessel diameter from photographs, as described below.[25] Similarly, few studies have evaluated the epidemiology of opacification of arteriolar wall,[54,58] due to difficulties in assessing the severity of opacification. In the Blue Mountains Eye Study in Australia, researchers graded this sign as “mild” or “marked” on standard photographs, and reported opacification of the arteriolar wall in 31.7% of participants, with the majority classified as “mild”.[59]

Finally, there are no population-based epidemiological studies on the less commonly seen hypertensive choroidopathy and optic neuropathy. Newer ocular imaging technology such as OCT-A, described below, may provide future population-based data on hypertensive choroidopathy, while hypertensive optic neuropathy is unlikely to be common in the general population.

2.3 Incidence

In contrast to prevalence data, there are substantially fewer studies reporting the natural history and incidence of hypertensive retinopathy in the non-diabetic general population. In the Beaver Dam Eye Study, the 5-year incidence of retinal focal arteriolar narrowing, AVN, and HMA was 9.9%, 6.5%, and 6.0%, respectively.[60] The study also reported that men had a 34% lower incidence of focal arteriolar narrowing, but a 30% higher incidence of AVN than women, after controlling for age,[60] but no statically significant gender difference in incidence of retinal HMA.[60] As expected, participants with known hypertension had a higher incidence of focal arteriolar narrowing and retinal HMA, after controlling for age, [60] although the incidence of AVN was higher only in women participants with hypertension.[60] Importantly, the investigators demonstrated that 60% of incident retinal HMA, 49% of incident focal arteriolar narrowing, and 37% of incident AVN were attributable to uncontrolled hypertension. This clearly indicates that lower BP levels and control of hypertension may reduce the risk of hypertensive retinopathy, which has implications for clinical management, as described below.

Other studies have reported similar results. In the Hoorn Study in the Netherlands, the 9-year incidence of retinal HMA was 7.3%, similar in men and women.[61] This study also reported that older age, hypertension, higher HbA_{1c} level, and waist-hip ratio were risk factors for developing retinal HMA.[61] In the Blue Mountains Eye Study, the 5-year incidence of retinal HMA was 9.7%.[62] Apart from age, no other risk factors were observed.[62] There are few population-based studies in other racial/ethnic groups. In the Beijing Eye Study in China, the 5-year incidence of retinal focal arteriolar narrowing, AVN, and HMA was 4.1%, 1.4%, and 3.3%, respectively.[63] Hypertension was also associated with incidence of focal arteriolar narrowing and HMA, but only marginally significant for AVN.

There are only two reported studies of longer-term incidence of hypertensive retinopathy signs beyond 10 years. In the Beaver Dam Eye Study, the 15-year cumulative incidence of retinal HMA was 14.2%.[64] Older age, higher BP, presence of CKD, and wider retinal arteriolar diameter were the associated factors for the 15-year incidence of retinal HMA.[64] Again, incidence was higher in those with uncontrolled hypertension at baseline, compared with those without hypertension,[64] indicating that control of BP may lower the risk of retinal HMA development. In the ARIC study, the

10-year incidence of focal arteriolar narrowing, AVN, and retinal HMA was 3.4%, 2.5%, and 2.2%, respectively.[65] This study also reported that higher baseline plasma fibrinogen and white cell counts were associated with incident focal arteriolar narrowing; antihypertensive medication use was associated with incident AVN, and higher diastolic BP, carotid intima media thickness, and white cell counts were associated with incident retinal HMA.[65]

2.4 Regression

Several studies also reported on the regression or disappearance of hypertensive retinopathy over time. In the Beaver Dam Eye Study, the 15-year disappearance rate of retinal HMA was 70%. This disappearance rate was associated with lower diastolic BP, higher serum high-density cholesterol level, lower cystatin C level and absence of CKD.[64] In the ARIC study, 50.3% of eyes with focal arteriolar narrowing, 40.7% with AVN and 65.9% with HMA did not have these signs over the 10-year period, suggesting a considerable degree of microvascular reverse remodeling.[65] In the Beijing Eye Study, among eyes with focal arteriolar narrowing, 76% were unchanged, while 1.8% progressed and 22.2% regressed.[63] Importantly, the rate of regression of focal arteriolar narrowing was significantly higher in participants with controlled (44.4%) than in uncontrolled (22.6%) and untreated (11.5%) hypertension.[63] Among eyes with AVN, the vast majority of eyes was unchanged (95%), 2.3% eyes progressed and 1.7% eyes regressed. [63] In contrast, among eyes with retinal HMA, 71.2% of eyes regressed to a normal status, supporting the concept that retinal HMA may be a transient phenomenon which may fluctuate with time, although the rate of regression of retinal HMA was not associated with BP levels or antihypertension treatment in the Beijing Eye Study.[63]

2.5 New concepts from recent epidemiological studies

While it is clear that hypertensive retinopathy is strongly correlated with BP levels, recent epidemiological studies have uncovered several new concepts. The first observation is that some signs of hypertensive retinopathy, specifically generalized and focal retinal arteriolar narrowing, may precede the clinical diagnosis of hypertension.[66-72] While the assessment of generalized arteriolar narrowing is difficult, studies using computer software (described below) to measure retinal vessel calibre have shown that

narrower retinal arteriolar calibre is associated with subsequent development of clinically diagnosed hypertension. This was confirmed in a meta-analysis of 10,229 participants without known prevalent hypertension, diabetes, or CVD at baseline.[73] This finding supports current hypotheses on the pathophysiology of hypertension. Retinal arteriolar narrowing may reflect the diffuse vascular remodelling and systemic peripheral vasoconstriction present in the early stages of hypertension.[74] As discussed, pre-clinical models and human studies suggest that both structural (e.g. morphological changes in resistance arteries) and functional microvascular remodelling (e.g. myogenic response) and noradrenaline sensitivity of vascular smooth muscle cells precede the development of clinical hypertension, consistent with retinal findings.[19,75-78] In fact, epidemiological studies in children as young as 5 years of age have already demonstrated an association between retinal arteriolar narrowing and BP in the higher percentiles of normal, indicating the impact of elevated BP on the microvasculature early in life,[79-82] which may "track" through to adulthood prior to development of clinical hypertension.

A second, and related, finding is that retinal arteriolar wall changes may be related to historical or past BP levels. Epidemiological studies have shown that generalized retinal arteriolar narrowing and AVN are associated with past BP levels,[26,83,84] suggesting that these arteriolar changes identified from subsequent retinal photography, may reflect cumulative effects from long-standing hypertension and are persistent markers of chronic vascular damage. Recent clinical studies have demonstrated that central BP, directly reflecting the BP load on target organs, is more closely associated with retinal arteriolar narrowing than brachial BP.[85] Masked hypertension as measured by ambulatory BP, is also associated with retinal arteriolar narrowing, reflecting vascular remodelling in the absence of raised BP in the clinic.[86,87] In contrast, it is likely that retinal microvascular lesions such as HMA mirror the effects of short-term BP changes, as it is more closely correlated with recent or concurrently measured BP.[28] This is consistent with clinical studies that show that HMA may regress with control of BP.

Finally, studies demonstrate that the retinal venular circulation, not traditionally considered part of the spectrum of hypertensive retinopathy, is also affected by BP. Using computer softwares, it has been shown that retinal venular widening (or dilation) is related to elevated BP, and subsequent risk of incident hypertension,[67,73] and incident

CVD events[73] (described further below). These findings suggest that in contrast to arterioles (which narrow), retinal venules (which dilate) exhibit different pathophysiological changes in response to BP and venules are not merely passive conductance vessels but an active dynamic component of the microcirculation. With additional data, retinal venular dilation could be considered a sign of hypertensive retinopathy in the future.

2.6 Relationship of hypertensive retinopathy with target organ damage and renal diseases

Cardiac and extracardiac hypertensive TOD is recognized as an intermediate step in the continuum of CVD and an independent predictor of CVD morbidity and mortality and all-cause death.[22] The presence of both mild and moderate hypertensive retinopathy has been associated with a range of markers of TOD and subclinical diseases (**Table 2**). These range from subclinical cerebral changes (cranial MRI-defined cerebral infarction, cerebral white matter lesions, cerebral atrophy and cerebral microbleeds[88-91]) to cardiac and large vessel changes (coronary artery calcification,[92] aortic stiffness,[86,93] left ventricular hypertrophy,[94-97] and carotid intima-media thickness[98]).

Hypertensive retinopathy is also closely linked to renal dysfunction, a key extracardiac TOD of hypertension.[47] Population-based studies have demonstrated a cross-sectional association between hypertensive retinopathy and chronic kidney disease (CKD) or renal impairment.[99-102] Some studies have also shown that hypertensive retinopathy is prospectively associated with incidence of CKD,[103] although findings are not consistent in other cohorts.[104,105] Finally, the coexistence of hypertensive retinopathy with other TOD (e.g., microalbuminuria and left ventricular hypertrophy) may indicate a higher risk of CVD.[106,107]

2.7 Relationship of hypertensive retinopathy with stroke and cerebrovascular diseases

The retinal vasculature is an extension of the cerebral vasculature, sharing embryological, anatomical and physiological features.[108] Thus, it is not unexpected that hypertensive retinopathy has been closely related to cerebrovascular diseases such as stroke. Large prospective population-based studies have indeed reported a relationship between hypertensive retinopathy with incident clinical stroke,[109-112] incident lacunar

stroke,[113] ischemic stroke[114] and self-reported stroke[115], even after controlling for classical stroke risk factors (**Table 3**). In addition to classic hypertensive retinopathy signs, some studies have also reported a consistent association of retinal venular widening, not traditionally considered part of hypertensive retinopathy, with incident stroke, cerebral infarction and intracerebral haemorrhage.[116,117]

Several studies have also suggested that different hypertensive retinopathy signs are associated with different stroke subtypes; for example, retinal arteriolar narrowing has been associated with lacunar stroke, whereas retinal HMA are linked with cerebral haemorrhages.[113,118-120] This suggests that retinal fundus examination may assist in the sub-classification of stroke.

Hypertensive retinopathy is also associated with dementia and cognitive impairment.[121,122] For example, hypertensive retinopathy was associated with decline in standardized cognitive test scores in the ARIC study, and in a large cohort study of older women.[123,124] The Rotterdam study, another large population-based prospective study, also reported the association of hypertensive retinopathy with prevalent dementia, and of retinal venular widening with incident dementia,[125,126] although the association with dementia subtypes (i.e., Alzheimer's disease versus vascular dementia) was not consistent.[126] Recent studies have shown that other computer software measures of the retinal vasculature (e.g. reduced retinal vascular fractal dimension) may also be associated with Alzheimer's disease.[127-129] These studies provide further support on the importance of microvascular pathophysiological pathways underlying cognitive impairment and dementia, and the potential use of retinal fundus photography for screening and risk stratification of neuro-cognitive disorders.[130]

2.8 Relationship of hypertensive retinopathy with coronary heart disease and heart failure

Prospective population-based studies have also demonstrated that various hypertensive retinopathy signs are associated with development of clinical CVD events such as coronary artery disease and heart failure (**Table 3**).[114,131-135] In the ARIC study, patients with retinal HMA were also three times more likely to develop congestive heart failure than those without retinopathy, even after controlling for CVD risk factors.[135] Other clinical studies have also found that hypertensive retinopathy was associated with

coronary artery atherosclerosis.[136,137] Interestingly, in one study, heart failure patients with preserved ejection fraction had a higher prevalence of hypertensive retinopathy than heart failure patients with reduced ejection fraction, possibly pointing to a different role of microvascular disease in the pathophysiology of heart failure subtypes.[138]

There has also been significant research in the relationship of computer software measured retinal vessel diameter with coronary artery disease.[139-141] In the ARIC study, persons with retinal arteriolar narrowing were more likely to develop incident coronary artery disease, with significant association only in women but not men, possibly reflecting the greater contribution of microvascular ischemia in women.[132] This observation was confirmed in a meta-analysis of 22,159 participants from 6 population-based studies that showed that the risk of coronary artery disease associated with retinal arteriolar narrowing was strongest among women.[142] In the ARIC study, narrower retinal arteriolar diameter was associated with incident heart failure.[134] Similar to stroke, prospective studies and a meta-analysis reported that retinal venular widening is also related to incident coronary artery disease.[134,142]

In addition to conventional retinal fundus photographs, clinical studies have also demonstrated changes in the dynamic response of retinal vessels to flickering light, reflecting endothelial dysfunction, which may be a predictor of CVD events in high-risk patients.[143]

2.9 Relationship of hypertensive retinopathy with all-cause and CVD mortality

Since the classic observations by Keith, Wagner and Barker in the 1930s,[49] hypertensive retinopathy signs are known to be prognostic indicators for mortality. In their study of 209 patients with untreated hypertension, the presence of optic disc oedema and HMA was correlated with very poor prognosis (5-year survival rate of 1% and 20%, respectively). The relationship of hypertensive retinopathy signs with all-cause, CVD and stroke mortality are shown in **Table 3**.[114,144-149] One study reported that patients with retinal HMA were more likely to die from coronary heart disease, with a risk similar to that of diabetes.[145] In a large study in Japan with nearly 90,000 participants, retinal HMA was associated with CVD mortality.[148] The association of different hypertensive retinopathy signs with CVD mortality was evaluated in the Beaver Dam Eye Study.[146] While the relationship of moderate hypertensive retinopathy (retinal

HMA) with CVD mortality was seen across the entire participant age range of 43-84 years, mild hypertensive retinopathy (generalized and focal arteriolar narrowing, AVN) was associated with CVD mortality only in younger participants aged 43-74 years of age.[146]

There are fewer studies of severe or malignant hypertensive retinopathy, but patients with optic nerve head oedema resulting from malignant hypertension (hypertensive optic neuropathy) have a very high risk of acute encephalopathy, heart failure and renal dysfunction if left untreated.[41,44,52]

In summary, over the past few decades, data from large population-based epidemiological studies show that hypertensive retinopathy signs are common in the general non-diabetic adult population and are associated with BP control. They are correlated with cardiac and extracardiac TOD manifestations of hypertension and the presence of hypertensive retinopathy is associated with higher risk of stroke, CVD events and mortality.

3. Mechanisms/Pathophysiology

3.1 Hypertensive retinopathy

The pathophysiology of hypertensive retinopathy can be broadly divided into different stages of disease development, corresponding to clinical findings and classification.[150] The changes relate to “vasoconstrictive”, “sclerotic” and “exudative” phases which classically occur sequentially in response to chronically elevated BP. Initially, physiological vasospasm and vasoconstriction of the retinal arterioles occur early in response to elevated BP (“vasoconstrictive” phase). Increase in vasomotor tone and the myogenic physiological response result in narrowing of retinal arterioles seen clinically as generalized retinal arteriolar narrowing. With persistently elevated BP over time, thickening of the intima and hyperplasia of the media wall occurs, with hyaline degeneration, which leads to the subsequent “sclerotic” phase. These changes can be observed clinically as more severe generalized and localized areas (focal) of retinal arteriolar narrowing, and hyaline changes in the arteriolar wall itself which become more opaqued clinically (opacification of arteriolar wall, described as “silver” or “copper wiring” or “altered arteriolar light reflexes”). In turn, narrowed and sclerosed

arterioles become more rigid and compress adjacent retinal venules resulting in AVN. Over time, chronically sustained BP elevation results in tissue ischemia and disruption of the blood–retinal barrier. In this "exudative" phase, pathological changes such as necrosis of smooth muscle and endothelial cells, exudation of blood and lipids, and retinal nerve fibre layer ischaemia are observed. These exudative changes are observed clinically as retinal HMA, hard exudates, and cotton-wool spots.[22]

These stages are not always sequential in time, and it is not uncommon to observe patients with acutely raised BP who only have retinal HMA reflecting the "exudative" phase without retinal arteriolar narrowing or AVN, signs of the earlier "sclerotic" phase. It is also increasing clear that elevated BP alone does not explain all the changes observed in hypertensive retinopathy. Animal models of hypertension and histopathologic studies have shown that other related processes occur prior to changes in the vascular structure of the retina, including inflammation,[151] impaired nitric oxide generation in endothelial cells and resulting endothelial dysfunction,[152] angiogenesis,[153] and oxidative stress.[154]

3.2 Hypertensive choroidopathy

Traditionally, hypertensive choroidopathy is thought to be due to choroidal ischemia resulting from elevated BP, which leads to fibrinoid necrosis at the level of the choriocapillaris and changes in the overlying retinal pigment epithelium and neural retina. Clinically, these are seen as Elschnig spots and Siegrist streaks in the fundus (**Figure 5**). Newer imaging modalities such as OCT and OCT-A have now allowed more direct assessment of choroidal changes in hypertension. As the choroid is a vascular tissue, the choroid is highly responsive to BP changes, and thus, choroidal thickening may represent hyperperfusion and increased flow, while choroidal thinning may indicate ischaemia and reduced flow. Both features appear to be present in hypertension. Saito et al. observed increased choroidal blood flow and choroidal thickening in the acute phase of hypertensive chorioretinopathy.[155] Over time, increased pulsatility in penetrating small blood vessels as a result of conduit artery stiffening and increased pulse pressure induces microvascular injury leading to remodelling, endothelial dysfunction, and ischaemia as discussed earlier in this paper, and rarefaction of smaller arterioles and capillaries.[156] Mulè et al. studied 158 consecutive hypertensive subjects and found choroidal thinning with higher 24-hour pulse pressure that reflects

arterial stiffness.[156] Thus, choroidal hyperperfusion may be followed by injury resulting from both increased flow,[155]and enhanced pulsatility contributing to further injury. This is followed by the effect of the myogenic reflex that induces vasoconstriction and impaired perfusion and tissue exchange, with enhanced oxidative stress in the vascular wall, all leading to microvascular rarefaction, reduced flow and choroidal thinning as a later expression of chronic hypertension.[156]

Recently, Mulè et al. studied 100 essential hypertensive patients (65 without CKD, and 35 in stages 1−3 CKD) and showed that subjects with CKD had thinner choroids, with choroidal thickness correlating positively with eGFR and negatively with urinary albumin excretion after accounting for age and other confounders.[157] This suggests a close relationship between changes in the choroidal circulation of the eye and the renal function, again emphasising choroidal thinning as a potential sign of generalized vascular injury in hypertension.[157] Indeed, a relationship between choroidal thickness and renal hemodynamics was also reported in subjects with primary hypertension who underwent Doppler evaluation of renal hemodynamics and ocular OCT imaging.[158] A thinner choroid was independently associated with a higher renal resistive index, indicating increased renal vascular resistance as a result of vascular injury in subjects with essential hypertension, which was confirmed in multivariate analyses. Thus, the ocular and the renal microvasculatures remodel in parallel in hypertension associated with pulsatile pressure and flow changes that through impaired perfusion lead to oxidative stress and endothelial dysfunction.[158] Studies of the systemic circulation in hypertension have shown that angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers, that is the blockade of the renin-angiotensin-system, results in correction of vascular remodeling and endothelial dysfunction together with correction of BP.[159-161] İçel et al. studied 40 newly diagnosed primary hypertensive patients and 21 healthy volunteers who were treated with perindopril arginine or amlodipine.[162] Using OCT, they showed an increase in choroidal thickness with perindopril arginine in the group of patients with primary hypertension, while no significant change occurred in the amlodipine group. Thus, similarly to the systemic vasculature, choroidal microvessels respond with correction of remodeling to inhibition of the renin-angiotensin system. In summary, these findings suggest that the use of OCT to measure choroidal thickness may be another means to quantify the severity of

hypertension in the eye. Whether OCT could be used to aid in risk stratification and hypertension management is a potential area of future research

3.3 Hypertensive optic neuropathy and malignant hypertensive retinopathy

Hypertensive optic neuropathy, manifested by bilateral optic disc swelling, is caused by severely elevated BP, and is classified as the "malignant" hypertensive retinopathy stage. The exact pathogenesis of optic disc swelling secondary to severe hypertension remains elusive, although Hayreh has suggested that ischemia similar to anterior ischemic optic neuropathy plays a major role in the optic disc oedema seen in hypertensive optic neuropathy.[4,163] While early capillary leakage as a result of hyperperfusion is usually asymptomatic, irreversible visual loss may develop secondary to vasoconstriction and impaired perfusion of the optic nerve head. Additionally, raised intracranial pressure and hypertensive encephalopathy may occur severely elevated BP and may be associated with bilateral optic disc oedema (papilloedema). These combined mechanisms likely all contribute to the optic disc oedema that occurs with malignant hypertensive retinopathy.[164] These changes are closely related to concurrent hypertensive acute TOD in the brain and kidneys.[165] Malignant hypertensive retinopathy may regress progressively once antihypertensive treatment is initiated and usually does not persist for more than 2-3 months. However, permanent ocular sequelae, mostly ischemia not only of the optic nerve, but also of the choroid and retina, may develop, with irreversible visual loss.

3.4 Genetic risk factors

It is unclear if genetic mechanisms play a role in predisposition to hypertensive retinopathy. Genetic epidemiology studies have provided inconclusive results thus far. A population-based genome-wide association study showed that retinal venular diameter was associated with some novel loci.[166] Further analysis of the same cohort demonstrated genome-wide significant association of retinal venular diameter with greater African ancestry at chromosome 6p21.1 among hypertensive individuals.[167] The angiotensin-converting enzyme gene polymorphism has also been linked with retinal arteriolar narrowing.[168] Others studies have reported isolated genetic loci associated with retinal arteriolar calibre and hypertensive retinopathy signs.[169,170] Future genetic studies on hypertensive eye disease, including whole exome or genome studies and

mendelian randomisation, may provide novel insights into the contribution of genetic mechanisms on the microcirculatory changes of hypertension and CVD.

4. Diagnosis, screening and prevention

4.1 Clinical assessment and presentation

Hypertensive retinopathy is typically diagnosed based on a history of hypertension, and on the presence of typical retinopathy signs as shown in **Table 1**, which also shows the traditional two four-grade Keith–Wagener–Baker and the three-grade Wong-Mitchell classification system.[49,171] Specifically, for the Wong-Mitchell classification, signs of mild hypertensive retinopathy include generalized and focal arteriolar narrowing, AVN, retinal arteriolar wall opacification ("silver" or "copper" wiring), or a combination of these signs (**Figure 2**), while moderate hypertensive retinopathy includes mild signs plus retinal HMA (**Figure 3**). Finally, in severely elevated BP, patients may have malignant retinopathy, which includes signs of moderate retinopathy with hypertensive optic neuropathy and optic disc swelling (**Figure 4**).

Hypertensive choroidopathy is characterized by Elschnig spots, which appear as deep, round, and gray-yellow lesions at the level of the retinal pigment epithelium and Siegrist streaks, which are linear hyperpigmented streaks along choroidal arterioles (**Figure 5**). Hypertensive choroidopathy is thought to be more common in younger individuals whose choroidal blood vessel are more pliable.[172] In severe cases, findings of serous retinal or retinal pigment epithelium detachments may develop, which can lead to vision loss.[164,172,173]

4.2 Imaging tests

Retinal fundus photography

Digital retinal fundus photography is used in many clinical settings to objectively document the presence of hypertensive retinopathy signs and in order to monitor their regression with anti-hypertensive treatment.

In research settings, computer softwares have also been developed to quantitatively measure the retinal vessel width (i.e. retinal arteriolar and venular diameter) for

documentation of generalized arteriolar narrowing.[25,174,175] The relationship of changes in retinal arteriolar and venular diameter to BP, hypertensive TOD and CVD risk have already been described above. In addition to the measurement of retinal vessel diameter, newer softwares allow the assessment of geometric patterns of the retinal vasculature, such as vessel tortuosity, fractal dimension, branching angles and vascular length-to-diameter ratio (e.g. SIVA (Singapore I Vessel Assessment) software, VAMPIRE software (Vascular Assessment and Measurement Platform for Images of the REtina) and QUARTZ (Quantitative Analysis of Retinal Vessel Topology and Size)).[54,93,176-179] These newer parameters, based on Murray's principle that deviations from optimal vascular pattern reflect reduced flow efficiency, may also be indicators of vascular damage.[180] Current versions of retinal vessel softwares, which are largely semi-automated, are not yet practical for routine clinical care, although fully automated versions are being developed.

Optical coherence tomography (OCT) and OCT-angiography (OCT-A)

OCT is a routinely used non-invasive optical imaging instrument that utilises a low-coherence light source near the infra-red spectrum to penetrate biological tissue,[181] providing cross-sectional images of the retinal and choroidal layers. Recent studies using OCT have shown reduced retinal and choroidal layer thickness measured in hypertensive patients, with correlation to other systemic TOD and retinal dysfunction.[182-185] Complications of hypertensive choroidopathy such as macular serous retinal detachment and choroidal ischaemic damage to the retinal pigment epithelium can also be assessed by OCT.[186,187]

OCT-A is a newer technology based on the principle of mapping red blood cell movement over time by comparing sequential OCT sagittal-scans at a given cross-section. Itcan be used to map the retinal and choroidal capillary network without the administration of intravenous dye.[188,189] A range of OCT-A measures reflecting reduced retinal (e.g. vessel density) and choriocapillaris flow (e.g., vessel density, vessel length, areas of signal voids or deficits) have been studied in hypertensive patients.[190-195] For example, a study found that OCT-A measured decreased choriocapillaris vessel density and vessel length correlated with hypertensive retinopathy severity.[192] Others have shown that the area of choriocapillaris flow deficit correlated with 24-hour ambulatory BP, lower estimated glomerular filtration rate and other risk factors (e.g., diabetes, use

of calcium channel blockers) in persons with hypertension.[193,196,197] In a case report, OCT-A demonstrated the presence of choriocapillaris flow deficit in a patient with hypertensive choroidopathy, and the areas of OCT-A flow deficit were validated and co-localized with hypofluorescent areas identified on intravenous indocyanine fundus angiography.[198] Another group observed localized ischaemic areas in the retina caused by impaired perfusion of the deep retinal vascular complex in hypertensive patients without retinopathy,[199] suggesting that retinal ischaemia may already be present before clinical retinopathy signs.[200] Several qualitative pathological signs have also been documented (e.g., focal capillary sparsity, scattered microangiomas, and focal capillary nonperfusion) with OCT-A in persons with hypertension.[201] **Figures 6-7** illustrate examples of reduced retinal capillary density and larger choriocapillaris flow deficits in patients with hypertension assessed by OCT-A. Several studies also demonstrated alterations in the retinal and choroidal capillary network in subjects with CKD.[202,203] These findings highlight the potential role of OCT-A to study early retinal and choroidal capillary changes related to hypertension and TOD. There remains, however, no studies that have shown OCT-A changes predictive of clinical CVD events. Such studies are needed before OCT-A assessment can be considered useful for hypertension management.

4.5 Differential diagnoses

The diagnosis of hypertensive retinopathy is typically based on direct observation of the classic signs shown in **Table 1** in patients with elevated BP or a history of hypertension. However, several conditions can also result in retinal signs that are similar to, and sometimes difficult to distinguish from, hypertensive retinopathy. Isolated retinal microaneurysms, retinal haemorrhages, hard exudates and cotton-wool spots can be detected frequently in the non-hypertensive (and non-diabetic) adult general population. Distinguishing hypertensive from diabetic retinopathy is sometimes challenging in persons with both hypertension and diabetes (**Figure 8A**), but certain retinal signs are more specific to hypertension[204] (e.g., retinal arteriolar wall changes such as AVN) whereas others are more suggestive of diabetes (e.g., retinal HMA and hard exudates in the absence of retinal arteriolar wall changes).[205] Optic disc swelling is a more specific sign of malignant hypertension whereas macular oedema is more common in diabetic retinal disease. Finally, the development of new vessels, or neovascularization is often

associated with diabetes (**Figure 8B**), and is not commonly seen in individuals with hypertension. Other ocular conditions with alterations in retinal vessels or retinal haemorrhages that can resemble hypertensive retinopathy and hypertensive chorioretinopathy include retinal artery occlusion, retinal vein occlusion, macroaneurysms, retinal artery emboli, ocular ischaemic syndrome, anaemia and other blood dyscrasias, leukaemia and radiation retinopathy (**Supplementary Figures 1-8**). Often, the clinical history along with the presence of elevated BP and the absence of other systemic diseases will help distinguish hypertensive retinopathy from the aforementioned conditions.

4.6 Screening and prevention

While most clinicians do not routinely screen for hypertensive retinopathy signs in the management of hypertension,[206] many international hypertension guidelines, such as the US Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC), the ESC/ESH, the American College of Cardiology (ACC)/American Heart Association (AHA), and National Institute for Health and Care Excellence (NICE)[44,207-209] continue to emphasize that hypertensive retinopathy is an indicator of TOD, and that its presence should be an indication for a more aggressive treatment of these hypertensive patients.[208]

The ESC/ESH guideline recommends that patients with suspected hypertensive emergency (either a systolic BP ≥180 mm Hg or diastolic BP ≥120 mm Hg) evaluated in an emergency department should undergo comprehensive evaluation including systematic retinal examination.[44] According to the NICE guideline, a retinal examination should be offered to all patients with hypertension to assess the presence of hypertensive retinopathy.[209] The 2020 International Society of Hypertension Global Hypertension Practice Guidelines recommend that retinal examination be offered to all patients with grade 2 hypertension, ideally by experienced clinicians or alternative techniques (e.g. digital retinal cameras) where available.[210]

There is evidence that a retinal examination for hypertensive eye disease would influence treatment decisions beyond other typical measures of TOD risk. A study of 280 hypertensive patients found that hypertensive retinopathy was an isolated phenomenon with respect to other TODs, and that the percentage of patients with

hypertension needing treatment with antihypertensive medication rises from 3 to 14% when hypertensive retinopathy is considered as a treatment indication. This suggests that routine retinal examination would help physicians consider initiating treatment in patients not yet on medication, or could warrant treatment intensification in those already on BP treatment.[211]

In summary, for certain groups of patients such as those with hypertensive emergencies, given a high prevalence of moderate and malignant hypertensive retinopathy,[212] a retinal examination is highly recommended and should be routinely performed. For the general patients with hypertension, a retinal examination could be useful for risk stratification and treatment decisions.

5. Management of hypertensive eye disease

The principle medical treatment for hypertensive eye disease is primarily focused upon lowering BP, based on established guidelines for management of hypertension. Regression of hypertensive retinopathy signs in direct response to BP reduction has already been demonstrated in clinical studies,[213-215] including diabetic populations.[216,217] Importantly, many population-based studies showed that control of BP is associated with a lower risk of developing hypertensive retinopathy or regression of these signs.[63,64] Furthermore, one study of 133 patients with newly-diagnosed untreated hypertension has shown that regression of hypertensive retinopathy is concurrently associated with significantly better outcomes for left ventricular hypertrophy and other TOD.[218] This supports the concept that regression or reduction of severity of TOD is a useful intermediate endpoint for assessing the efficacy of BP-lowering medications.[44]

With regards to visual outcomes, most patients with mild or moderate hypertensive retinopathy do not have visual symptoms and are not at increased risk of visual impairment. However, patients with malignant hypertensive retinopathy may report decreased vision, and irreversible profound visual loss is possible. Similarly, patients with hypertensive choroidopathy should be referred to emergency departments for urgent anti-hypertensive management,[219-222] and may be considered for more aggressive ocular intervention such as intravenous anti-VEGF treatment.[219]

Finally, whether specific anti-hypertensive agents have particular value in the treatment of hypertensive retinopathy is unclear. However, there is evidence, as referred to above, that because the retinal and choroidal vasculature and the systemic microvasculature remodel in parallel in hypertension, associated with pulsatile pressure and flow changes that impair tissue perfusion and result in enhanced oxidative stress and endothelial dysfunction,[158] agents that target vascular remodelling and endothelial dysfunction may be superior to agents that do not have these effects. Because ACE inhibitors and angiotensin receptor blockers (ARB) correct vascular remodeling and endothelial dysfunction systemically together with the lowering of BP, these agents may be useful for treatment of hypertensive retinopathy and choroidopathy.[159-161] Indeed, ACE inhibitors appear to have a more favourable effect on the retinal vasculature.[213-215] İçel et al. have further demonstrated, in a study of hypertensive patients treated with either perindopril arginine or amlodipine, that whereas perindopril arginine treatment reverses choroidal thinning, suggesting that vascular changes are improved and/or reversed, there was no choroidal benefit with amlodipine.[162] It remains to be demonstrated whether retinal vessels respond similar to choroidal microvessels, which is likely but unproven. In addition, introduction of anti-hypertensive medications should be considered if signs of hypertensive retinopathy is detected in patients with presumed white coat hypertension.[223]

In summary, while the benefits of anti-hypertensive treatment for patients with elevated BP and hypertensive eye disease is clear, there are currently no randomized controlled studies that have evaluated whether specific anti-hypertensive hypertension will reverse established hypertensive eye disease, or that regression in severity of ocular changes is an indicator of better systemic and visual outcomes. Thus, most guidelines (e.g., the American College of Cardiology/American Heart Association,[207] European Society of Cardiology/European Society of Hypertension[44] and International Society of Hypertension Guidelines[224] for management of hypertension) do not provide specific guidelines for the treatment of hypertensive retinopathy, but recommend that the goal of treatment for all hypertensive patients be generally less than 140/90 mm Hg, ideally close to- or around 130/80 mm Hg. Depending on the cardiovascular risk of a specific patient, starting with lifestyle modification including weight control, remaining active or exercising, reducing alcohol intake, and importantly reducing salt intake and following a healthy diet is recommended. In addition, for those patients whose BP is not

controlled with these measures or who are at higher cardiovascular risk, treatment with antihypertensive drugs is indicated including renin-angiotensin inhibitors, thiazide or thiazide-like diuretics, or calcium channel antagonists, often needed in combination, without a preference usually for a first line therapy among these. Other agents are then added if BP is not controlled.

As emphasized above, more important than the treatment of hypertensive retinopathy *per se* is the value of hypertensive retinopathy to guide BP targets.[74] **Figure 9** shows a proposed management flow chart for hypertensive eye disease, modified based on the Wong-Mitchell three-grade classification.[50] Patients with mild retinopathy usually only require routine care according to established hypertension guidelines. Patients with moderate retinopathy may benefit from a more detailed systematic assessment of CVD risk (e.g., carotid or cardiac imaging) and, if clinically indicated, appropriate risk reduction therapy. Patients with malignant retinopathy will need urgent anti-hypertensive management, most often in hospital settings.[50]

6. Quality of life

Patients with hypertension have worse health-related quality of life,[2,225] and those with other TOD such as CKD are also known to have poorer quality of life.[226,227] However, there are no data on the impact of vision loss in patients with hypertensive eye disease. For hypertensive retinopathy, the major reason for the paucity of studies is that in early stages, vision alteration or loss (e.g. vision dimming) is mild and may not be noticeable even though hypertensive retinopathy is common in people age older than 40 years. On the other hand, while it is expected that hypertensive choroidopathy and hypertensive optic neuropathy may significantly affect vision, they are uncommonly seen and recruitment of patients for quality of life studies may be difficult. Research on the impact and treatment of hypertensive eye disease on health-related quality of life could be conducted as part of studies evaluating other TOD.

7. Outlook

7.1 Updating the classification systems

The validity of the new classification systems (i.e. Wong-Mitchell classification) for cardiovascular risk stratification is still yet to be tested in large prospective studies. The

inclusion of new measurements from retinal fundus photography using computer softwares (e.g. retinal-vessel diameter) is also unclear. OCT and OCT-A are now widely available and potentially allow early signs of hypertensive eye disease (e.g., retinal venular dilation, choroidal thickening or thinning, and retinal capillary microvascular ischaemia) to be objectively documented. These signs could be incorporated into a new classification system that is broader than the current system which only reflects one spectrum of retinal changes. However, determination of the value of these newer signs of hypertensive ocular damage requires prospective studies to document their presence and inclusion is associated with other TOD and CVD risk.

7.1 Telemedicine

The development of telemedicine and tele-screening with retinal photography for diabetic retinopathy is well established and is shown to be cost-effective and to reduce the incidence of vision loss due to diabetic retinopathy.[228-230] Further telemedicine strategies can facilitate detection of other ocular pathologies, including hypertensive retinopathy.[228,231,232] Numerous handheld and tabletop digital nonmydriatic fundus cameras are now commercially available and provide excellent quality fundus photography, and are easy to use. More recently, smartphone camera technology for retinal fundus photography has shown great potential for eye disease screening due to its low-cost, portability, ubiquity, easy acquisition and wireless data transfer capabilities.[233,234] In a study in an emergency department setting, smartphone technology to detect hypertensive retinopathy was shown to be reliable in patients with acute hypertension, highlighting this promising technology.[235] The infrastructure for telemedicine (e.g. 5G networks, cloud computing) is set to expand and scale in the coming decades.

7.2 Artificial intelligence

Artificial intelligence is now routinely applied to medical image interpretation. In particular, DL, a branch of AI with convolutional neural networks, has been developed for detection of eye diseases from retinal fundus photographs and OCT studies.[236,237] Highly accurate AI-DL systems can be used for automated detection of diabetic retinopathy in patients with diabetes,[238,239] detection of papilloedema and optic nerve abnormalities,[240] and a range of other conditions, such as CKD, anaemia, carotid artery

atherosclerosis, coronary artery calcium score and specific CVD risk factors (e.g., BP, body mass index, smoking and HbA1c).[241-247] It is likely that an AI-DL algorithm will be able to accurately detect features of hypertensive retinopathy, choroidopathy andc optic neuropathy, providing easy diagnosis of hypertensive eye diseases by non-specialists (e.g., general physicians) as well as risk of CVD prediction. AI-DL algorithms may even allow prediction of hypertension years before elevated BP is detected and allow further individualization of hypertension prevention.

7.3 New ocular imaging modalities

Novel ocular imaging technologies such as measurement of wall-to-lumen ratio of retinal arterioles using scanning laser Doppler flowmetry,[248] cellular-level retinal imaging using adaptive optics,[249] measurement of retinal vessel oxygen saturation using retinal oximetry[250], and assessment of flicker light-induced vasodilation using dynamic retinal vessel analysis[251] are being explored to correlate retinal changes with systemic hypertension. Advances in non-invasive ocular and retinal imaging technologies hold promise for further examining and studying hypertensive changes in the eye and systemic end-organ damage, in addition to clinical funduscopic examination and retinal photography (**Figure 1**).

7.4 Other research advances

There are additional research areas for hypertensive eye disease. First, using big data in biobanks with >100,000 of images, causal relationships between gene polymorphisms, hypertension prevalence and severity, and hypertensive retinopathy phenotypes could be explored by Mendelian randomization studies. Mendelian randomization can be used to test causal relationships between risk factors and phenotypes such as BP. While single nucleotide polymorphisms (SNPs) have been identified in genome-wide association study, these SNPs reflect lifetime exposure to a risk factor. Mendelian randomization will provide evidence of possible causal relationships between these risk factors and a disease using genetic variants. Importantly, Mendelian randomization is not affected by confounding or reverse causality, because of the random independent assortment of genetic variants. Finally, there are no data on vision loss and health-related quality of life related to hypertensive eye disease. Including these measures in clinical trials of

patients with hypertension will increase our understanding of the broader impact of hypertensive eye disease on patient outcomes.

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Table 1. The grading and clinical features of the Keith–Wagener–Baker and Wong-Mitchell systems.

Keith–Wagener–Baker grading System (1939)		**Mitchell-Wong grading system (2004)**		**Key pathophysiological changes and signs**
Grade	**Clinical Features**	**Grade**	**Clinical Features**	
1	Mild to moderate narrowing or sclerosis of the arterioles	Mild	Generalized arteriolar narrowing, focal arteriolar narrowing, arteriovenous nicking, opacification of the arteriolar wall (silver or copper wiring), or a combination of these signs	Retinal vascular re-modeling Retinal arteriolar wall signs
2	Moderate to marked narrowing of the arterioles Local and/or generalized narrowing of arterioles Exaggeration of the light reflex Arteriovenous crossing changes or nicking			
3	Retinal arteriolar narrowing and focal constriction, retinal oedema, cotton-wool patches, retinal haemorrhages, hard exudates	Moderate	Signs of mild retinopathy plus retinal haemorrhages (blot, dot, or flame-shaped), microaneurysms, cotton-wool spots, hard exudates, or a combination of these signs	Retinal tissue damage with breakdown of blood-retinal barrier Retinal microvascular signs
4	Grade 3 plus optic disc swelling	Malignant	Signs of moderate retinopathy plus optic disc oedema, in the presence of severely elevated blood pressure	

Table 2. Relationship of hypertensive eye disease with other target organ damage and subclinical atherosclerotic diseases.

	Outcomes
Hypertensive retinopathy	
Mild	Left ventricular hypertrophy,[94,95,97] aortic stiffness[86,93]
	Chronic kidney disease,[101,252] albuminuria[102]
Moderate	Cerebral infarcts, lacunar infarcts and white matter lesions,[91] cerebral white matter lesions[88]
	Left ventricular hypertrophy,[96] carotid artery plaques,[53] coronary artery calcification,[92] Carotid intima-media thickness[53,98]
	Incident chronic kidney disease,[103] progression of chronic kidney disease,[106,107] development of renal dysfunction,[100] micro/macroalbuminuria[99]
Malignant	Higher rehospitalization rates[253]
Eye conditions related to hypertension	
Retinal vein occlusion	Carotid artery plaques,[254] renal dysfunction[255]
Retinal arteriolar emboli	Carotid artery plaques,[254] chronic kidney disease[8]

Table 3. Relationship of hypertensive eye disease with clinical cardiovascular disease (CVD) events and mortality.

	Outcomes
Hypertensive retinopathy	
Mild	**Stroke:** Incident stroke,[109] incident ischemic stroke,[114] incident lacunar stroke,[113] incident cerebral infarction,[111] stroke mortality,[256]
	CVD: Incident CVD event,[106,114] incident coronary heart disease,[114,132] incident heart failure, [134] coronary heart disease mortality,[256] self-reported coronary heart disease[115]
	Mortality: All-cause mortality[114] and CVD mortality[146,148]
Moderate	**Stroke:** Incident stroke,[88,109,110,112] incident lacunar stroke,[113] incident cerebral infarction[111] prevalent stroke,[53] stroke mortality,[149] self-reported stroke[115]
	CVD: Incident congestive heart failure,[135] coronary heart disease mortality[145]
	Mortality: CVD mortality,[146,147] all-cause mortality[147]
	Others: Prevalent dementia,[125,126] cognitive decline[123,124]
Malignant	**Mortality**[49]

Eye conditions related to hypertension	
Retinal vein occlusion	**Stroke:** Incident stroke,[257-259] incident of cerebrovascular accident,[260] prevalent cerebrovascular disease[261]
	CVD: Prevalent CVD[262] Incident acute myocardial infarction,[263] history of congestive heart failure, [261] history of angina and heart attack[264,265]
	Mortality: All-cause mortality[266-268] and CVD mortality[269,270]
Retinal arteriolar occlusion/emboli	**Stroke:** Prevalent stroke,[8,271] stroke mortality[271,272], incident stroke,[273-276] prevalent stroke[277]
	CVD: Prevalent CVD[278] Prevalent coronary heart disease,[254] history of coronary artery disease,[271,279] history of any vascular event (angina, myocardial infarct, stroke) or history of vascular surgery[280,281]
	Mortality: All-cause mortality[271]

Figure Legends

Figure 1. The effect of elevated blood pressure on the eye. Non-invasive retinal imaging technologies hold promise for further examining hypertensive changes in the eye and systemic end-organ damage.

Figure 2. Examples of mild grade of hypertensive retinopathy. **Panel A** showing arteriovenous nicking (AVN, black arrows) and focal arteriolar narrowing (FAN, white arrow). **Panel B** showing opacification (silver or copper wiring) of the arteriolar wall (OAW, black arrows).

Figure 3. Examples of moderate grade of hypertensive retinopathy. **Panel A** showing a flame-shaped retinal hemorrhage (RHx, black arrow) and a cotton-wool spot (CWS, white arrow). **Panel B** shows a combination of retinal haemorrhages (blot, dot, or flame-shaped), microaneurysms, cotton-wool spots and hard exudates. **Panel C** shows moderate grade of hypertensive retinopathy from wide-field retinal photography.

Figure 4. An example of malignant hypertensive retinopathy. **Panel A.** Signs of moderate retinopathy in combination with swelling of the optic disc (white star) are present from fundus photographs. **Panel B** Optical coherence tomography of the same patient showing changes in the retinal layered structure (hard exudates, HE, yellow arrows; subretinal fluid, SRF, red arrow) and optic disc (optic disc edema, blue arrows) in a cross-sectional view. **Panel C** Cranial computed tomography scan of patient showing concomitant intracranial hemorrhage secondary to hypertension.

Figure 5. An example of hypertensive choroidopathy. **Panel A** Ultra-wide field retinal imaging showing Elschnig spots (white boxes) and Siegriest streaks (black box). **Panel B** Fundus autofluorescence showing hypoautofluorescence of Elschnig spots and Siegriest streaks. Some Elschnig spots are not well seen on color images (yellow boxes).

Figure 6. Optical coherence tomography angiography (OCTA; 3 × 3 mm area at macula) of superficial capillary plexus (**A, D and G**), deep capillary plexus (**B, E and H**) and choriocapillaris (**C, F and I**) of a hypertensive with normal blood pressure (Top panel; **A**–**C**), a hypertensive with moderately elevated blood pressure (Middle panel; **D**–**F**), and a hypertensive with severely elevated blood pressure (Bottom panel; **G**–**I**), showing the presence of reduced retinal vessel density in the superficial capillary plexus and deep capillary plexus as well as larger sized choriocapillaris flow deficits in the hypertensive with high blood pressure.

Figure 7. Measurement of choriocapillaris flow deficits from optical coherence tomography angiography image. Color-coded maps indicate regions of flow deficits (**B, D and F**; color coded) of choriocapillaris of a healthy control individual (Top panel; **A**–**B**), a hypertensive with well-controlled blood pressure (Middle panel; **C**–**D**), and a hypertensive with poorly controlled blood pressure (Bottom panel; **E**–**F**), showing the presence of larger sized choriocapillaris flow deficits in a hypertensives with severely elevated BP (**F**; labelled as yellow). The presence of flow deficits can be seen as areas of dark regions in the angiogram (**A, C** and **E**) and its sizes are color-coded (**B, D** and **F**).

Figure 8. Two case examples of diabetic retinopathy. **Panel A** shows moderate non-proliferative diabetic retinopathy with microaneurysms and retinal hemorrhage (white boxes), cotton-wool spot (white arrows) and hard exudates (black boxes) in a patient with diabetes and hypertension. **Panel B** neovascularization (black box) in a patient with proliferative diabetic retinopathy.

Figure 9. Management flow chart.