

Hypertensive retinopathy revisited: some answers, more questions

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Hypertension is associated with cardiovascular risk and systemic target organ damage. Retinopathy is considered one of the indicators of target organ damage. This review focuses on recent studies on hypertensive retinopathy and their implications for clinical care. Early recognition of hypertensive retinopathy signs remains an important step in the risk stratification of hypertensive patients.

Guidelines (BHS IV)¹⁵ consider retinopathy as target organ damage, although again only for grades III and IV.

There are a number of considerations that may militate against systematic retinal examination in patients with hypertension. These include vague definitions and heterogeneous classifications of hypertensive retinopathy, making severity staging a largely arbitrary process, as well as the lack of well defined prognostic value for either systemic outcomes or visual impairment.

Hypertension is a worldwide problem that affects up to 50 million people in the United States and approximately one billion worldwide, and is the single most important modifiable risk factor for stroke.^{1–3} Even milder degrees of blood pressure elevation pose increased risk for cardiovascular events. Unfortunately, hypertension awareness, treatment, and control remain less than optimal.^{4–5} Hypertension acts as a silent killer many years before overt end organ damage is clinically apparent. Hence, the importance of refining risk stratification strategies to ensure reliable detection of hypertension related end organ damage before it becomes symptomatic.

The retina provides a window to study the human circulation. Retinal arterioles can be visualised easily and non-invasively and share similar anatomical and physiological properties with cerebral and coronary microcirculation.^{6–10}

DETECTION OF HYPERTENSIVE RETINOPATHY

Poorly controlled systemic hypertension causes damage to the retinal microcirculation, so that recognition of hypertensive retinopathy may be important in cardiovascular risk stratification of hypertensive patients.¹¹ However, there is no widely accepted classification or definition of hypertensive retinopathy. Various international management guidelines are not consistent in this respect. For example, the risk stratification table (table 1) from the European Society of Hypertension-European Society of Cardiology Guidelines (ESH-ESC 2003)¹² indicates that hypertensive retinopathy grades III and IV (as defined from table 2) are associated clinical conditions, while the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VII) in the United States indicates generically retinopathy (without mention of grade) as target organ damage.¹³ Additionally, the WHO International Society of Hypertension (WHO-ISH) 2003 statement¹⁴ and the British Hypertension Society 2004

EPIDEMIOLOGY

Several recent studies have shown that retinal microvascular changes can be reliably documented by retinal photographs.^{16–23} In general, reproducibility from photographs has been found to be excellent for well defined retinopathy signs (kappa values ranged from 0.80 to 0.99 for microaneurysms and retinal haemorrhages) and fair to moderate for other more subtle retinal arteriolar lesions (0.40–0.79 for arteriolar narrowing and arteriovenous nicking).²⁴

Furthermore, these studies suggest that generalised arteriolar narrowing could be estimated from an assessment of retinal vessel diameters on photographs by use of imaging software. The development of specific software packages have made it possible to objectively measure the arteriole to venule ratio (AVR) in selected standardised portions of the retina.^{16–17} This technique appears to have substantial reproducibility (intraclass correlation coefficient ranged from 0.80–0.99).^{17–20–23}

On the basis of retinal photography, retinal microvascular signs are common in adults 40 years of age and older, even in those without history of diabetes and hypertension. Both prevalence and incidence of between 2–15% have been reported for various retinal microvascular lesions.^{19–25}

WHAT RETINAL SIGNS ARE CLINICALLY USEFUL TO CLINICIANS FOR RISK ASSESSMENT?

Data from population based studies indicate that certain signs of hypertensive retinopathy (table 3) are associated with increased cardiovascular risk,

Abbreviations: ABPM, ambulatory blood pressure monitoring; AION, anterior ischaemic optic neuropathy; AMD, age related maculopathy; AVR, arteriole to venule ratio; BP, blood pressure; CHD, coronary heart disease; CVD, cardiovascular disease; IMT, intima-media thickness; LVH, left ventricular hypertrophy; MRI, magnetic resonance imaging; RAO, retinal arterial occlusion; RVO, retinal vein occlusion; WCH, white coat hypertension

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Table 1 Different prognostic classification of hypertensive retinopathy, according to the European Society of Hypertension-European Society of Cardiology (ESH-ESC) 2003 Guidelines, the JNC 7 Report, the British Hypertension Society (BHS) IV 2004 Guidelines, and the World Health Organization-International Society of Hypertension (WHO/ISH) 2003 statement on diagnosis and treatment of hypertension

ESH-ESC 2003 guidelines ¹²	JNC 7 report 2003 ¹³	WHO/ISH 2003 statement ¹⁴ and BHS IV 2004 guidelines ¹⁵
Associated clinical conditions Advanced retinopathy: haemorrhages or exudates, papilloedema	Target organ damage Retinopathy	Target organ damage Hypertensive retinopathy grade III or IV

independently of other risk factors.^{23–28} Generalised and focal retinal arteriolar narrowing has been shown to predict the risk of hypertension in normotensive people.^{29–31} Generalised arteriolar narrowing (fig 1), focal arteriolar narrowing, arteriovenous nicking (fig 2), opacity (copper wire) of arteriolar wall, or a combination of these (mild grade of retinopathy) have been associated with a mild increase (odds ratio greater than 1 but less than 2) of incident clinical stroke, coronary heart disease, and death. The Atherosclerosis Risk in Communities Study showed that generalised arteriolar narrowing of the retinal arterioles was associated with subsequent coronary heart disease in women (relative risk, 2.2; 95 confidence interval 1.0 to 4.6) but not in men (relative risk, 1.1; 95 confidence interval 0.7 to 1.8).³² Furthermore, in the ARIC Study generalised arteriolar narrowing of the retinal arterioles was found to be independently associated with increased risk for type 2 diabetes (odds ratio, 1.71; 95 confidence interval 1.13 to 2.57).³³

Haemorrhages (blot, dot, or flame shaped), microaneurysms, cottonwool spots, hard exudates (fig 3), or a combination of these signs (moderate grade of retinopathy) are more strongly associated (odds ratio of 2 or greater) with risk of incident clinical stroke,³⁴ presence and severity of magnetic resonance imaging (MRI) defined cerebral white matter lesions and cerebral atrophy defined on MRI,³⁵ reduced cognitive performance on standardised neuropsychological tests,^{36–37} and death from cardiovascular causes.²⁸ The ARIC Study reported that people with microaneurysms, retinal haemorrhages, and soft exudates were two to three times more likely to develop an incident clinical stroke over 3 years than people without these retinal lesions, independently of blood pressure, diabetes, cigarette smoking, elevated lipid levels, and other risk factors.³⁴ Furthermore, there was a multiplicative interaction between the presence of retinal microvascular changes and white matter lesions on the risk of stroke. The 5 year relative risk of stroke among participants who had both hypertensive retinopathy and cerebral lesions on MRI, compared with those who had neither of these findings, was 18.1 (confidence interval, 5.9 to 55.4);



Figure 1 Mild hypertensive retinopathy. Photograph shows generalised retinal arteriolar narrowing.



Figure 2 Mild hypertensive retinopathy. Photograph shows arteriovenous nicking (white arrow).

among participants who had white matter lesions only, the relative risk of stroke was 3.4 (confidence interval, 1.5 to 7.7).³⁵

In a nested case-control study in patients with age related eye diseases in Wisconsin (the Beaver Dam Eye Study) the presence of retinal microaneurysms, retinal haemorrhages, and retinal arteriolar narrowing was associated with a high

Table 2 The Keith, Wagener, and Barker¹¹⁷ hypertensive retinopathy classification (grade I-IV), based on the level of severity of the retinal findings

Grade	Classification	Symptoms
Grade I (mild hypertension)	Mild generalised retinal arteriolar narrowing or sclerosis	No symptoms
Grade II (more marked hypertension retinopathy)	Definite focal narrowing and arteriovenous crossings. Moderate to marked sclerosis of the retinal arterioles. Exaggerated arterial light reflex	Asymptomatic
Grade III (mild angiospastic retinopathy)	Retinal haemorrhages, exudates and cotton wool spots. Sclerosis and spastic lesions of retinal arterioles	Symptomatic
Grade IV	Severe grade III and papilloedema	Reduced survival

Table 3 Classification of hypertensive retinopathy by Wong and Mitchell²⁶

Grades	Description	Systemic associations
No retinopathy	No detectable retinal signs	None
Mild retinopathy (retinal arteriolar signs only) (figs 1, 2)	One or more of the following arteriolar signs: • Generalised arteriolar narrowing • Focal arteriolar narrowing • Arteriovenous nicking • Arteriolar wall opacity (silver wiring)	Modest* association with risk of clinical stroke, subclinical stroke, coronary heart disease, and mortality.
Moderate retinopathy (fig 3)	One or more of the following retinal signs: • Haemorrhage (blot, dot, or flame shaped) • Microaneurysm • Cottonwool spot • Hard exudates	Strong† association with risk of clinical stroke, subclinical stroke, cognitive decline, and cardiovascular mortality
Malignant retinopathy (fig 5)	Moderate retinopathy plus optic disc swelling‡	Strong association with mortality

*Modest: risk and odds ratios of >1 but <2. †Strong: risk and odds ratios of >2. ‡Anterior ischaemic optic neuropathy, characterised by unilateral optic disc swelling, visual loss, and sectoral visual field loss, should be excluded neuropathy, characterised by unilateral optic disc swelling, visual loss, and sectorial visual field loss, should be excluded.

10 year risk of stroke mortality.²⁸ In the Cardiovascular Health Study, people with similar signs of retinopathy were twice as likely to have a history of stroke as those who did not have these signs (odds ratio, 2.0; confidence interval, 1.1 to 3.6).²² Other population based studies reported that the risk of fatal and non-fatal stroke are two to three times as high in people do not have these signs, independently of cardiovascular risk factors.^{28 38}

WHY ARE SPECIFIC RETINAL SIGNS ASSOCIATED WITH DIFFERENT CARDIOVASCULAR COMPLICATIONS?

Population based studies reported that mild and moderate grades of retinopathy correlate with different main outcome measures.^{18 23 26 28 32-35} This requires a plausible interpretation. It is possible that different manifestations of hypertensive retinopathy do not originate from the same pathogenic mechanism, and therefore predispose to different levels of cardiovascular risk. An alternative explanation is that, from a quantitative point of view, a higher degree of generalised vascular damage might bring together more severe retinal findings and more frequent main outcome measures.

Findings from the ARIC, Blue Mountains Eye, and Beaver Dam Eye studies^{23 26 27 28} indicate that the pathogenesis of retinal arteriolar changes (focal narrowing, generalised arteriolar narrowing, and arteriovenous nicking) is distinct from that of more severe signs of hypertensive retinopathy (microaneurysms, haemorrhages, hard exudates, and cottonwool spots).



Figure 3 Moderate hypertensive retinopathy. Photograph shows cottonwool spots and retinal haemorrhages.

According to histopathological studies,³⁹ generalised retinal arteriolar narrowing and arteriovenous nicking seem to be related to chronically high blood pressure. In the ARIC Study, independently of blood pressure, generalised arteriolar narrowing was also related to systemic markers of inflammation, whereas arteriovenous nicking was related to markers of inflammation and endothelial dysfunction and may reflect persistent structural damage from these processes.^{23 27 28 40-42} Endothelial function of the retinal vasculature is impaired in early essential hypertension.⁴³ The role of nitric oxide in the maintenance of choroidal and retinal flow has been recently verified.⁴⁴⁻⁵⁰ L-NMMA reaction of retinal capillary flow is impaired in hypertensive patients⁴³ and in patients with type 1 diabetes a reduced response of choroidal flow to L-NMMA has also been observed.⁵¹ Additionally, arteriolar narrowing and arteriovenous nicking were inconsistently associated with diabetes, glucose, and glycosylated haemoglobin.²⁸

In contrast, hypertensive retinopathy was strong and consistently associated with diabetes, its duration, and its severity. In the ARIC Study hypertensive retinopathy was related to concurrent but not past blood pressure values.²⁹ Microaneurysms, retinal haemorrhages, and soft exudates are most commonly seen when there is a breakdown of the blood-retinal barrier.

Thus, a possible explanation for these data is that mild hypertensive retinopathy reflects cardiovascular disease (CVD) risk in relation to chronic effects of elevated blood pressure, whereas moderate grade of hypertensive retinopathy reflects CVD risk in relation to diabetes, glycaemia, and to recently diagnosed, more severe hypertension.^{28 52} Furthermore, the prognostic significance of specific retinal vascular abnormalities may vary with age. The fact that arteriovenous nicking was almost twice as frequent in younger people (6.5%) than older people (3.3%) who died of CVD causes is consistent with such a hypothesis.²⁸

HYPERTENSION AND DIABETES

Diabetes and hypertension are both vascular risk factors and may share similar pathophysiological mechanisms. Both conditions are also linked by the metabolic syndrome.^{53 54} The prevalence of diabetes among patients with hypertension is high,⁵⁵ and type 2 diabetes may remain unrecognised for years before being diagnosed.⁵⁶ When diabetes is associated with hypertension, cardiovascular risk rises exponentially and retinopathy becomes more severe and rapidly progressive. In turn, more tight control of blood pressure in

hypertensive diabetic people was shown to prevent cardiovascular events as well as deterioration of both retinopathy and visual acuity.^{57–59} Among the various pathophysiological mechanisms, endothelial dysfunction has been implicated in the pathogenesis of the metabolic syndrome and points to a link between diabetes and hypertension.^{60–61} It was observed⁵¹ that systemic and ocular haemodynamic reactivity to NO-synthase inhibition is reduced in patients with long standing insulin dependent diabetes mellitus, compared with healthy control subjects. The blunted response of retinal capillary flow to L-NMMA observed⁴³ in young hypertensive patients with essential hypertension indicates a reduced contribution of nitric oxide to the maintenance of retinal perfusion.⁴³ Therapy with AT1 receptor blocker candesartan celextil restored both the contribution of nitric oxide to the maintenance of retinal perfusion and nitric oxide dependent vasodilation in the retinal vasculature of patients with arterial hypertension.⁴³ Other mechanisms linking diabetes and hypertension are inflammatory processes and overt atherosclerosis.^{62–63}

DO RETINAL SIGNS CORRELATE WITH HYPERTENSION SEVERITY?

A correlation between retinal lesions, as detected by direct ophthalmoscopy, and left ventricular hypertrophy, as defined by echocardiography, was suggested⁶⁴ but the study was limited by the imprecision of clinical ophthalmoscopy in quantifying retinal arteriolar narrowing and by the rather small sample size. Some studies have linked renal dysfunction with retinal vascular changes,^{65–68} but the relation of early retinal vessel vascular changes and risk of cardiovascular complications is not well understood.

Recent findings from a clinical study⁶⁹ showed no significant relation between retinal microvascular changes (diffuse arteriolar narrowing, arteriovenous crossings), detected by qualitative examination of the fundus, and prognostically validated markers of target organ damage, such as 24 hour ambulatory blood pressure monitoring, 24 hour urine collection for microalbuminuria, echocardiography, carotid ultrasonography in early stages of untreated essential hypertension. Early retinal alterations were extremely frequent in this cohort of relatively young untreated subjects with recently diagnosed grade 1 or 2 hypertension. Furthermore, the prevalence of retinal microvascular abnormalities was much higher than that of left ventricular hypertrophy, carotid wall alterations, and microalbuminuria.^{69–71} Patients with arteriovenous crossings did not have more cardiac, carotid, and renal alterations compared with those without this retinal pattern. The distribution of retinal microvascular changes was similar in lower, intermediate, or higher tertiles of left ventricular mass.

THE ROLE OF SYSTEMIC HYPERTENSION AS A RISK FACTOR FOR OTHER EYE DISEASES SUCH AS GLAUCOMA OR AGE RELATED MACULAR DEGENERATION

In addition to hypertensive retinopathy, elevated blood pressure is a risk factor for many ocular conditions. These include anterior ischaemic optic neuropathy, retinal vein occlusion, retinal arteriolar emboli and, possibly, age related maculopathy (AMD) and glaucoma.⁷² With regard to AMD, the Framingham Study⁷³ reported an association of AMD with systemic hypertension, a relation that increased with the duration of the hypertension.⁷³ However, other studies have not found consistent relations. No such correlation was found for the development of the neovascularisation in the studies by Bressler,⁷⁴ the Eye Disease Case Control Study Group,⁷⁵ and the Beaver Dam Eye Study.⁷⁶ More recently, the Macular Photocoagulation Study⁷⁷ found a relative risk of 1.7 for the development of choroidal neovascularisation in

patients with definite systemic hypertension. Over 5 years, the incidence of choroidal neovascularisation was 49% among patients with definite hypertension versus 33% in patients without definite hypertension. The authors stressed the importance of high blood pressure on the prognosis of the fellow eye. With regards to glaucoma, a population based study⁷⁸ showed a modest positive association of primary open angle glaucoma with systolic and diastolic blood pressure. In another study,⁷⁹ however, no correlation was showed in the prevalence of arterial hypertension in primary and secondary open angle glaucoma.

Are retinal examinations more useful in specific subgroups of populations?

There is strong evidence that identifying and targeting subsets of hypertensive patients at highest risk improves the cost effectiveness of antihypertensive treatment.⁸⁰ Subjects with white coat hypertension (WCH) or masked hypertension—that is, the phenomenon of consistently elevated clinic blood pressure levels but normal 24 hours ambulatory blood pressure monitoring,⁸¹ may represent an intermediate group between healthy people and sustained hypertensives as far as target organ damage and cardiovascular risk is concerned. Prevalence of this condition is quite variable, depending of the selection groups, suggesting a range between 12%–30%, being more common in the elderly⁸² and among females.⁸² Previous studies have suggested that WCH is associated with end organ damage.^{82–83}

The presence of hypertensive retinopathy in WCH may suggest an indication to antihypertensive therapy.

Evidence is increasing that even mild blood pressure (BP) elevation can have an adverse effect on vascular structure and function in asymptomatic young people. High BP in childhood had been considered a risk factor for hypertension in early adulthood. The retinal examination is recommended to identify retinal vascular changes in young patients with co-morbid risk factors and BP 90th–94th percentile and in all patients with BP \geq 95th percentile.^{84–89} A previous study reported a prevalence of 41% for the arteriolar narrowing and of 8% for arteriovenous nicking, as defined by retinal photographs, in a cohort of 97 children and adolescents with essential hypertension.⁹⁰ Further longitudinal studies will be necessary to determine how these retinal vascular signs progress over time in juveniles with essential hypertension and whether the abnormalities are of prognostic importance.⁹¹ Finally, it is unclear whether retinal examination would confer a greater benefit in women and black people.²⁶

WHAT SHOULD CLINICIANS DO WITH THE CURRENT EVIDENCE?

On the basis of the available data we propose a flow chart about the supplemental risk assessment by the ophthalmoscopic consultation in hypertensive subjects (fig 4). The strongest evidence of the usefulness of hypertensive retinopathy for risk stratification is based on its association with stroke (tables 3–5).^{26–34–35} In the presence of equivocal signs (borderline or inconsistent hypertension or WCH with no other evidence of target organ damage) or visual symptoms, an examination by the ophthalmologist may be useful. The presence of retinopathy may be an indication for initiating antihypertensive treatment.^{12–13–26} For hypertensive patients grade 2¹² without overt target organ damage ophthalmological referral may also be useful. The presence of retinopathy may be an indication for more aggressive intervention on associated cardiovascular risk factors and co-morbidities and has an important practical impact for treatment decisions (for example, antihypertensive and anti-platelet aggregation) and for close follow up. Furthermore, for some patients, ophthalmic consultation may be useful to rule out diabetic

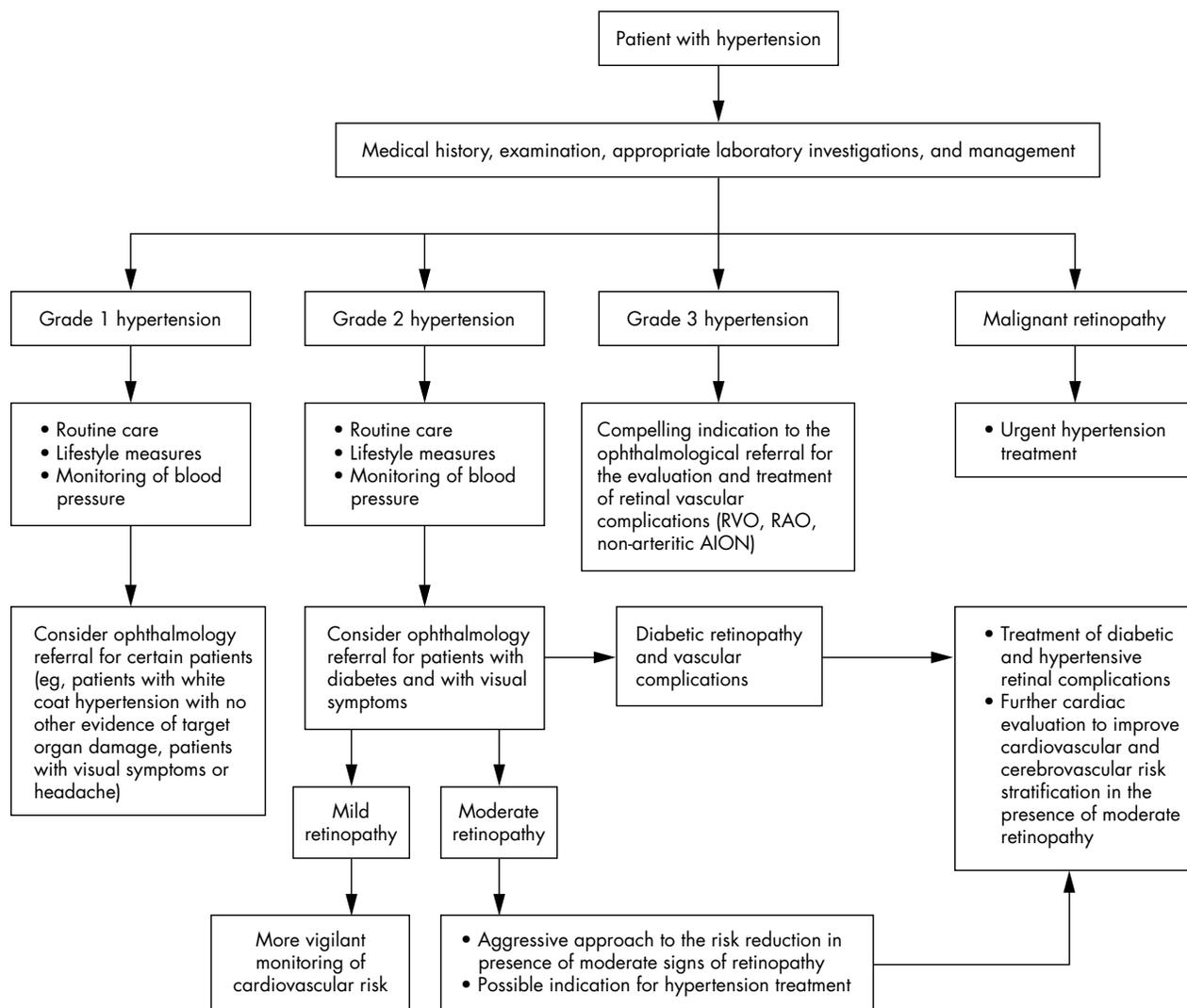


Figure 4 Flow chart: supplemental risk assessment by retinal examination.

retinopathy, retinal vein occlusion, anterior ischaemic optic neuropathy, or retinal arterial occlusion.^{44 47 26} For all grade 3 hypertensive patients¹² there are compelling indications for an ophthalmological referral (fig 5) for evaluation and treatment of retinal vascular complications.⁹² In WCH the ophthalmological referral may be indicated when there is no other evidence of target organ damage. In the presence of both mild and moderate (table 3) retinal signs, pharmacological treatment may be warranted. In the presence of moderate retinal signs (table 3) ophthalmologists may refer people for further cardiac evaluation to improve the cerebrovascular risk stratification.⁹³

LIMITATIONS OF AVAILABLE DATA

Epidemiological studies provide additional insight that arteriolar constriction and narrowing may have a critical role in the development of hypertension. However, caution must be applied to the interpretation of these data.

Firstly, raised intraocular pressure may affect retinal arteriolar calibre. The ARIC Study did not include an assessment of IOP.^{94–96}

Secondly, photographs were not synchronised with the cardiac cycle and vessel diameter may vary because of pulsatility. A variation of 2% to 17% has been described.^{97 98} However, because photography was independent of any

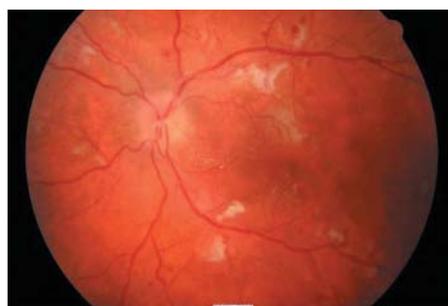


Figure 5 Malignant hypertensive retinopathy. Photograph shows multiple cotton wool spots, retinal haemorrhages, optic disc swelling, and macular star.

subject characteristics, this variation, at most, would have caused random misclassification. The optimal conditions for taking measurements, with reference to posture,⁹⁹ blood pressure,¹⁰⁰ and autonomic nervous system,¹⁰¹ also need to be standardised. Furthermore, pregnancy induces modifications on the vascular dynamics.¹⁰²

Thirdly, the overall prevalence of retinopathy signs in some recently reported studies may be too high.^{69 70} It is unclear

Table 4 Mild hypertensive retinopathy (retinal arteriolar signs only)

Sign	Diagnosis	Histopathology correlations	Clinical correlations	Future research
Generalised arteriolar narrowing	<ul style="list-style-type: none"> Qualitative examination of retinal photographs^{69,70} Computer assisted fundus image analysis and AVR calculation in selected standardised portions of the retina^{16,17} 	<ul style="list-style-type: none"> Vasoconstrictive phase: vasospasm and an increase in retinal arteriolar tone⁶ Sclerotic phase: intimal thickening, hyperplasia of the tunica media, and hyaline degeneration in the subsequent sclerotic stage⁶ 	<ul style="list-style-type: none"> Risk of hypertension (odds ratio, 1.62; CI 95% 1.21 to 2.18)²⁹⁻³¹ Risk of stroke (relative risk, 1.24, CI 95% 0.66 to 2.31)^{34,35} Risk of CHD in women (relative risk, 1.37; CI 95% 1.08 to 1.72)³² Risk of diabetes mellitus (odds ratio, 1.71, CI 95% 1.13 to 2.57)³³ Relation to stiffness of the carotid arteries¹¹⁶ Risk of cognitive impairment:modest association³ 	<ul style="list-style-type: none"> Clinical validation of the AVR Clinical significance (a) CVD evaluation in presence of retinal microvascular lesions (b) Potential value of specifically targeting the microcirculation in the treatment of hypertension Prevention (c) Role of retinal photography for CVD risk stratification
Focal arteriolar narrowing	<ul style="list-style-type: none"> Constricted area of two thirds or less the width of proximal and distal vessel segments¹⁷ 	<ul style="list-style-type: none"> Areas of localised vasoconstriction evaluated on the disc and within 1/2 DD of its margin zone¹⁷ 	<ul style="list-style-type: none"> Risk of any stroke (relative risk crude, 1.57, CI 95%, 1.0 to 2.45)^{34,35} Risk of cognitive impairment:modest association³⁶ 	<ul style="list-style-type: none"> Prevention Usefulness of focal arteriolar narrowing evaluation in the cerebrovascular risk stratification
Arteriovenous nicking	<ul style="list-style-type: none"> Present if seen in at least one of the temporal quadrants; definite if the venous blood column was tapered on both sides of its crossing under an arteriole; EDTRS standard photograph^{9,17} 	<ul style="list-style-type: none"> Sclerotic phase: intimal thickening, hyperplasia of the tunica media, and hyaline degeneration in the subsequent sclerotic stage⁶ 	<ul style="list-style-type: none"> Risk of any stroke (relative risk, 2.21, CI 95%, 1.44 to 3.38)^{34,35} Risk of cognitive impairment:modest association³⁶ 	<ul style="list-style-type: none"> Prevention Usefulness of arteriovenous nicking evaluation in the cerebrovascular risk stratification in hypertensives

how these changes were defined and how signs were classified. Moreover, the terminology used is neither consistent nor comparable with data from other population based studies. The recommendations issued by ESH-ESC 2003¹² do not take in account recent data from epidemiological studies, but are derived only from the conclusion of one clinical study.⁷⁰ Fourthly, there are no reliable clinical data to relate signs of retinopathy with other prognostically validated markers of target organ damage, such as intima-media thickness (IMT), left ventricular hypertrophy (LVH), and ABPM. Reclassification of cardiovascular risk recently proposed,⁶⁹ taking into account the evaluation of the arteriovenous nicking, is biased by the cross sectional design of the study. Finally, from a methodological viewpoint, retinal photographs in those large population based studies were evaluated in standardised settings, which are typical of

clinical research but may not be transferred easily to everyday practice.

WHAT ARE FUTURE RESEARCH QUESTIONS?

Researchers should develop a common and standardised photographic classification of the retinal signs similar to diabetic retinopathy.

Secondly, the ARIC study offers insights that support the hypothesis that microvascular disease may have a more prominent role in the development of myocardial ischaemia and coronary heart disease (CHD) in women. However, this and other population base studies are prevented from making a more definite conclusion because they assessed retinal microvasculature, not the coronary or cerebral microcirculation. In addition, data from population base studies do not necessary imply a cause (generalised arteriolar narrowing)

Table 5 Moderate hypertensive retinopathy

Sign	Diagnosis	Histopathology correlations	Clinical correlations	Future research
Microaneurysm	Present v absent	Exudative phase: disruption of blood-barrier, degeneration of vascular smooth muscle and endothelial cell necrosis leading to blood and lipid exudation and ischaemia ⁶	<ul style="list-style-type: none"> Risk of any stroke (relative risk , 6.11; CI 95% 3.72 to 10.05)³⁴ Risk of cognitive impairment :strong association³⁵ 	<ul style="list-style-type: none"> Prevention Is retinal photography useful in the measurement of stroke risk?
Retinal haemorrhage (blot, dot, or flame,shaped)	<ul style="list-style-type: none"> Blot Flame shaped Both 	Exudative phase	<ul style="list-style-type: none"> Risk of any stroke (relative risk, 6.44; CI 95% 3.61 to 11.49)³⁴ Risk of any stroke (relative risk, 6.38; CI 95% 2.97 to 13.73)³⁴ Risk of cognitive impairment:strong association³⁵ 	<ul style="list-style-type: none"> Prevention (a) Is retinal photography useful in the measurement of stroke risk? (b) Cognitive impairment may be amenable to treatment and prevented strategies targeted at vascular diseases
Soft exudates	Present v absent	Ischaemia of the nerve fibre layer	<ul style="list-style-type: none"> Risk of any stroke (relative risk 7.80, CI 95% 4.07 to 14.96)³⁴ Risk of cognitive impairment:strong association³⁵ 	<ul style="list-style-type: none"> Prevention It is important to replicate some of these findings in other populations to assess the associations of retinal microvascular disease to different stroke subtypes and to other clinical and subclinical cerebral disorders with a supposed microvascular aetiology

and effect (incident CHD and stroke) relation. Thus, it is unclear why the association of generalised arteriolar narrowing was not associated with incident CHD in men. Further investigation is required to support the hypothesis that microvascular disease has a more prominent role in development of myocardial ischaemia and CHD in women.¹⁰³ Other unmeasured factors (for example, use of vasodilator medications, diurnal and nocturnal fluctuations of blood pressure) associated with generalised arteriolar narrowing of retinal arterioles might have caused incident CHD or the stroke.¹⁰³

Thirdly, the ARIC Investigators have shown that generalised retinal arteriolar narrowing may precede the onset of diabetes mellitus in middle aged people and may even have a role in its initial development. However, the authors have only shown a short term association between generalised arteriolar narrowing of the retinal arterioles and incident diabetes. Further studies are required to determine whether longer term associations do exist.

Fourthly, there has not been a consistent demonstration that these retinal signs have independent predictive value and that the addition of retinal photography may help to optimise global risk evaluation in primary hypertension and modify the therapeutic decisions.²⁶

Finally, population based studies suggest that narrowed arterioles are associated with the development of hypertension and therefore that small vessel disease may be a target for antihypertensive treatment.^{104–107} Thus, there is a need to evaluate whether specific therapy focused on the retinal microcirculation can reverse¹⁰⁸ change in retinopathy or reduce retinal microvascular damage,^{43 109} and, if so, whether this approach will also result in a reduced cardiovascular risk.

NEW WAYS TO DETECT HYPERTENSIVE MICROVASCULAR DAMAGE: GENERALISED ARTERIOLAR NARROWING AS AN EXAMPLE OF FUTURE TECHNOLOGY

A quantitative way of assessing one of the microvascular changes—generalised arteriolar narrowing in the retina—has been developed and used in population based studies.^{16 19–22} The photographs were digitised and the diameters of individual arterioles and venules coursing through a zone located ½–1 disc diameter from the optic disc margin were measured with a dedicated software and summarised as an arteriole-venule ratio (AVR). Use of the ratio was introduced to counter several potential problems. Firstly, it introduces some adjustment for the wide range of vessel diameter in the normal population. Secondly, by virtue of being a ratio it offers some protection against several potential problems: (a) variable magnification caused by differences in refractive error among individuals, (b) apparent broadening of vessel calibre as a result of poor photographic focus or ocular media clarity, and (c) differences among graders regarding the precise determination of the vessel edge.

It remains unclear what exactly the separate arteriolar and venular diameters contributed to the AVR and what kind of vascular disease this ratio precisely reflects. In the ARIC, Beaver, and Blue Mountains Eye Study the authors attributed a lower AVR to generalised arteriolar narrowing. Data from the Rotterdam Study indicate that the AVR does not reflect only generalised arteriolar narrowing but also a separate contribution from venular diameters. The authors hypothesise other pathogenic mechanisms related to the disruption of the endothelial surface layer and to inflammatory processes.^{110–112}

Findings from the Wisconsin Epidemiologic Study of Diabetic Retinopathy^{113 114} showed that in eyes with non-proliferative diabetic retinopathy, measurement of venous dilation may add prognostic information independently of

the severity scale. Wider retinal venular diameters have been suggested to reflect hyperperfusion resulting from both hyperglycaemia and retinal hypoxia.¹¹⁵ Thus, in future research, more attention should be paid to the role of venules in vascular disease.

CONCLUSION

In conclusion, hypertensive retinopathy remains a recognised manifestation of target organ damage in hypertensive patients.¹¹⁸ Digital retinal photography aimed at the automated measurement of retinal arteriolar diameter is useful in research on the microvascular contributions to clinical cardiovascular disease. In the future, a retinal examination might acquire a specific indication to predict (that is, consider CVD evaluation in presence of retinal microvascular lesions) and prevent (that is, role of retinal photography for CVD risk stratification) metabolic and/or cardiovascular events in the general population, even in the absence of overt hypertension or diabetes.

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