Hypertensive retinopathy revisited: some answers, more questions

A Grosso, F Veglio, M Porta, F M Grignolo, T Y Wong

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. Even milder degrees of blood pressure elevation pose increased risk for cardiovascular events. Hypertension awareness, treatment, and control remain less than optimal. 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.

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. 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) indicates that hypertensive retinopathy grades III and IV (as defined from table 2) are associated with increased 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. Additionally, the WHO International Society of Hypertension (WHOISH) 2003 statement and the British Hypertension Society 2004 Guidelines (BHS IV) 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.

EPIDEMIOLOGY

Several recent studies have shown that retinal microvascular changes can be reliably documented by retinal photographs. 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 microvascular signs (kappa values ranged from 0.40 to 0.79 for arteriolar narrowing and arteriovenous nicking). 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. This technique appears to have substantial reproducibility (intraclass correlation coefficient ranged from 0.80–0.99).

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.

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, 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

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
independently of other risk factors. Generalised and focal retinal arteriolar narrowing has been shown to predict the risk of hypertension in normotensive people. 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). 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). 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, presence and severity of magnetic resonance imaging (MRI) defined cerebral white matter lesions and cerebral atrophy defined on MRI, reduced cognitive performance on standardised neuropsychological tests, and death from cardiovascular causes. 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. 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 white matter lesions only, the relative risk of stroke was 3.4 (confidence interval, 1.5 to 7.7). 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>
<thead>
<tr>
<th>Grade</th>
<th>Classification</th>
<th>Symptoms</th>
</tr>
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<tbody>
<tr>
<td>Grade I (mild hypertension)</td>
<td>Mild generalised retinal arteriolar narrowing or sclerosis</td>
<td>No symptoms</td>
</tr>
<tr>
<td>Grade II (more marked hypertension retinopathy)</td>
<td>Definite focal narrowing and arteriovenous crossings. Moderate to marked sclerosis of the retinal arterioles. Exaggerated arterial light reflex</td>
<td>Asymptomatic</td>
</tr>
<tr>
<td>Grade III (mild angioplastic retinopathy)</td>
<td>Retinal haemorrhages, exudates and cotton wool spots. Sclerosis and spastic lesions of retinal arterioles</td>
<td>Symptomatic</td>
</tr>
<tr>
<td>Grade IV</td>
<td>Severe grade III and papilloedema</td>
<td>Reduced survival</td>
</tr>
</tbody>
</table>
10 year risk of stroke mortality. 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). Other population based studies reported that the risk of fatal and non-fatal stroke are two to three times as high in people who do not have these signs, independently of cardiovascular risk factors.

**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. 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 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 cotton-wool spots).

According to histopathological studies, 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. Endothelial function of the retinal vasculature is impaired in early essential hypertension. The role of nitric oxide in the maintenance of choroidal and retinal flow has been recently verified. L-NMMA reaction of retinal capillary flow is impaired in hypertensive patients and in patients with type 1 diabetes a reduced response of choroidal flow to L-NMMA has also been observed. Additionally, arteriolar narrowing and arteriovenous nicking were inconsistently associated with diabetes, glucose, and glycosylated haemoglobin.

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. 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. 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.

**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. The prevalence of diabetes among patients with hypertension is high, and type 2 diabetes may remain unrecognised for years before being diagnosed. 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 cardio-
vascular 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 observed
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
24 hour urine collection for microalbuminuria, echocardio-
graphy, carotid ultrasonography in early stages of untreated
essential hypertension. Early retinal alterations were extre-
mely frequent in this cohort of relatively young untreated
patients with arterial hypertension.45 Other mechanisms linking diabetes and hypertension are
inflammatory processes and overt atherosclerosis.62–65

**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 dysfunc-
tion with retinal vascular changes,67–68 but the relation of
early retinal vessel vascular changes and risk of cardiovas-
cular 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, echocardio-
graphy, carotid ultrasonography in early stages of untreated
essential hypertension. Early retinal alterations were extre-
mely frequent in this cohort of relatively young untreated
patients 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 microalbumi-

nuria.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.74 However, other studies
have not found consistent relations. No such correlation was
found for the development of 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
gle 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
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 cardiovas-
cular 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.83 Previous studies have suggested that
WCH is associated with end organ damage.84–85

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 ≥95th percentile.84–86 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.87 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 impor-
tance.88 Finally, it is unclear whether retinal examination
would confer a greater benefit in women and black people.89

**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 ophthalmo-
scopic consultation in hypertensive subjects (fig 4). The
strongest evidence of the usefulness of hypertensive retino-
pathy for risk stratification is based on its association with
stroke (tables 3–5).12,34,35 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 ophthalmologi-
cal 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

retinopathy, retinal vein occlusion, anterior ischaemic optic neuropathy, or retinal arterial occlusion. For all grade 3 hypertensive patients there are compelling indications for an ophthalmological referral (fig 5) for evaluation and treatment of retinal vascular complications. 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.

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.

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. However, because photography was independent of any subject characteristics, this variation, at most, would have caused random misclassification. The optimal conditions for taking measurements, with reference to posture, blood pressure, and autonomic nervous system, also need to be standardised. Furthermore, pregnancy induces modifications on the vascular dynamics.

Thirdly, the overall prevalence of retinopathy signs in some recently reported studies may be too high. It is unclear...
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 are not based on a more definite conclusion because they assessed retinal angiography, not the coronary or cerebral microcirculation. In addition, data from population base studies do not necessarily imply a cause (generalised arteriolar narrowing).

### Table 4: Mild hypertensive retinopathy (retinal arteriolar signs only)

<table>
<thead>
<tr>
<th>Sign</th>
<th>Diagnosis</th>
<th>Histopathology correlations</th>
<th>Clinical correlations</th>
<th>Future research</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generalised arteriolar narrowing</td>
<td>- Qualitative examination of retinal photographs&lt;sup&gt;16, 70&lt;/sup&gt;</td>
<td>- Vasospastic phase: increase in retinal arteriolar tone&lt;sup&gt;6&lt;/sup&gt;</td>
<td>- Risk of hypertension (odds ratio, 1.62; CI 95% 1.21 to 2.18)&lt;sup&gt;26&lt;/sup&gt;</td>
<td>Clinical validation of the AVR</td>
</tr>
<tr>
<td></td>
<td>- Computer assisted fundus image analysis and AVR calculation in selected standardised portions of the retina&lt;sup&gt;4, 17&lt;/sup&gt;</td>
<td>- Sclerosing phase: intimal thickening, hyperplasia of the tunica media, and hyaline degeneration in the subsequent sclerotic stage&lt;sup&gt;17&lt;/sup&gt;</td>
<td>- Risk of stroke (relative risk, 1.24; CI 95% 0.66 to 2.31)&lt;sup&gt;31&lt;/sup&gt;</td>
<td>Clinical significance (a) CVD evaluation in presence of retinal microvascular lesions</td>
</tr>
<tr>
<td></td>
<td>- Relationship of stiffness of the carotid arteries&lt;sup&gt;18&lt;/sup&gt;</td>
<td>- Risk of CHD in women (relative risk, 1.37; CI 95% 1.08 to 1.72)&lt;sup&gt;32&lt;/sup&gt;</td>
<td>- Risk of cognitive impairment: modest association&lt;sup&gt;19&lt;/sup&gt;</td>
<td>Prevention (c) Role of retinal photography for CVD risk stratification</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Risk of diabetes mellitus (odds ratio, 1.71; CI 95% 1.13 to 2.57)&lt;sup&gt;33&lt;/sup&gt;</td>
<td>- Risk of cognitive impairment: modest association&lt;sup&gt;19&lt;/sup&gt;</td>
<td>Prevention (c) Role of retinal photography for CVD risk stratification</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Relationship of stiffness of the carotid arteries&lt;sup&gt;19&lt;/sup&gt;</td>
<td>- Risk of cognitive impairment: modest association&lt;sup&gt;19&lt;/sup&gt;</td>
<td>Prevention (c) Role of retinal photography for CVD risk stratification</td>
</tr>
<tr>
<td>Focal arteriolar narrowing</td>
<td>- Constricted area of two thirds or less the width of proximal and distal vessel segments&lt;sup&gt;19&lt;/sup&gt;</td>
<td>- Areas of localised vasoconstriction evaluated on the disc and within ½ of the margin zone&lt;sup&gt;17&lt;/sup&gt;</td>
<td>- Risk of any stroke (relative risk crude, 1.57; CI 95%, 1.0 to 2.45)&lt;sup&gt;36&lt;/sup&gt;</td>
<td>Prevention (c) Role of retinal photography for CVD risk stratification</td>
</tr>
<tr>
<td>Arteriovenous nicking</td>
<td>- 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&lt;sup&gt;17&lt;/sup&gt;</td>
<td>- Sclerosing phase: intimal thickening, hyperplasia of the tunica media, and hyaline degeneration in the subsequent sclerotic stage&lt;sup&gt;17&lt;/sup&gt;</td>
<td>- Risk of any stroke (relative risk, 2.21; CI 95%, 1.44 to 3.38)&lt;sup&gt;36, 38&lt;/sup&gt;</td>
<td>Prevention (c) Role of retinal photography for CVD risk stratification</td>
</tr>
</tbody>
</table>

#### Table 5: Moderate hypertensive retinopathy

<table>
<thead>
<tr>
<th>Sign</th>
<th>Diagnosis</th>
<th>Histopathology correlations</th>
<th>Clinical correlations</th>
<th>Future research</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microaneurysm</td>
<td>Present v absent</td>
<td>- Exudative phase: disruption of blood-barrier, degeneration of vascular smooth muscle and endothelial cell necrosis leading to blood and lipid exudation and ischaemia&lt;sup&gt;18&lt;/sup&gt;</td>
<td>- Risk of any stroke (relative risk, 6.11; CI 95% 3.72 to 10.05)&lt;sup&gt;34&lt;/sup&gt;</td>
<td>Prevention (a) Is retinal photography useful in the measurement of stroke risk?</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Risk of cognitive impairment: strong association&lt;sup&gt;35&lt;/sup&gt;</td>
<td>Prevention (a) Is retinal photography useful in the measurement of stroke risk?</td>
</tr>
<tr>
<td>Retinal haemorrhage (blot, dot, or flame shaped)</td>
<td>Blot v Flame shaped v Both</td>
<td>- Exudative phase</td>
<td>- Risk of any stroke (relative risk, 6.44; CI 95% 3.61 to 11.49)&lt;sup&gt;34&lt;/sup&gt;</td>
<td>Prevention (a) Is retinal photography useful in the measurement of stroke risk?</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Risk of any stroke (relative risk, 6.38; CI 95% 2.97 to 13.73)&lt;sup&gt;34&lt;/sup&gt;</td>
<td>Prevention (a) Is retinal photography useful in the measurement of stroke risk?</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Risk of cognitive impairment: strong association&lt;sup&gt;35&lt;/sup&gt;</td>
<td>Prevention (b) Cognitive impairment may be amenable to treatment and prevented strategies targeted at vascular diseases</td>
</tr>
<tr>
<td>Soft exudates</td>
<td>Present v absent</td>
<td>- Ischaemia of the nerve fibre layer</td>
<td>- Risk of any stroke (relative risk 7.80; CI 95% 4.07 to 14.96)&lt;sup&gt;34&lt;/sup&gt;</td>
<td>Prevention (c) 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</td>
</tr>
</tbody>
</table>

**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 microvascularity, not the coronary or cerebral microcirculation. In addition, data from population base studies do not necessarily imply a cause (generalised arteriolar narrowing)
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. 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. 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.

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. Thus, there is a need to evaluate whether specific therapy focused on the retinal microcirculation can reverse change in retinopathy or reduce retinal microvascular damage, 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. 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.

Findings from the Wisconsin Epidemiologic Study of Diabetic Retinopathy 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. 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. 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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Hypertensive retinopathy revisited: some answers, more questions

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Br J Ophthalmol 2005 89: 1646-1654
doi: 10.1136/bjo.2005.072546

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