Hypertensive retinopathy revisited: some answers, more questions

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

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.

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 with well defined 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 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.

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 (intra-class correlation coefficient ranged from 0.80–0.99).17–20

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.16–25

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.
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 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

<table>
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<tr>
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<tbody>
<tr>
<td>Associated clinical conditions</td>
<td>Target organ damage</td>
<td>Target organ damage</td>
</tr>
<tr>
<td>Advanced retinopathy: haemorrhages or exudates, papilloedema</td>
<td>Retinopathy</td>
<td>Hypertensive retinopathy grade III or IV</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Grade</th>
<th>Classification</th>
<th>Symptoms</th>
</tr>
</thead>
<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 angiospastic 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>

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

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

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**Table 3 Classification of hypertensive retinopathy by Wong and Mitchell**

<table>
<thead>
<tr>
<th>Grades</th>
<th>Description</th>
<th>Systemic associations</th>
</tr>
</thead>
<tbody>
<tr>
<td>No retinopathy</td>
<td>No detectable retinal signs</td>
<td>None</td>
</tr>
<tr>
<td>Mild retinopathy (retinal arteriolar signs only)</td>
<td>One or more of the following arterial signs:</td>
<td>Modest association with risk of clinical stroke, subclinical stroke, coronary heart disease, and mortality.</td>
</tr>
<tr>
<td></td>
<td>• Generalised arterial narrowing</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Focal arterial narrowing</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Arteriovenous nicking</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Arterial wall opacity (silver wiring)</td>
<td></td>
</tr>
<tr>
<td>Moderate retinopathy</td>
<td>One or more of the following retinal signs:</td>
<td>Strong association with risk of clinical stroke, subclinical stroke, cognitive decline, and cardiovascular mortality</td>
</tr>
<tr>
<td>(fig 3)</td>
<td>• Haemorrhage (blot, dot, or flame shaped)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Microaneurysm</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Cottonwool spot</td>
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<tr>
<td></td>
<td>• Hard exudates</td>
<td></td>
</tr>
<tr>
<td>Malignant retinopathy</td>
<td>Moderate retinopathy plus optic disc swelling</td>
<td>Strong association with mortality</td>
</tr>
<tr>
<td>(fig 5)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

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**Figure 3** Moderate hypertensive retinopathy. Photograph shows cottonwool spots and retinal haemorrhages.
hypertensive diabetic people was shown to prevent cardio-
vascular events as well as deterioration of both retinopathy
and visual acuity. 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. 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
to L-NMMA observed in young hypertensive patients with
essential hypertension indicates a reduced contribution of
nitric oxide to the maintenance of retinal perfusion. Therapy
with AT1 receptor blocker candesartan cilexetil 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.
Other mechanisms linking diabetes and hypertension are
inflammatory processes and overt atherosclerosis.

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 suggested 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, but the relation of
early retinal vessel vascular changes and risk of cardiovas-
cular complications is not well understood.

Recent findings from a clinical study 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
hypertension. Early retinal alterations were extre-
meely frequent in this cohort of relatively young untreated
subjects with systemic hypertension—that is, the phenomenon of consistently
raised clinic blood pressure levels but normal 24 hours
ambulatory blood pressure monitoring 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 on the selection groups, suggesting a
range between 12%–30%, being more common in the elderly
and among females. Previous studies have suggested that
WCH is associated with end organ damage.

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. 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. 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. Finally, it is unclear whether retinal examination
would confer a greater benefit in women and black people.

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 ophthalm-
oscopic 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). 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. For hypertensive patients
with grade 2 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. Second, 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 2003 do not take account recent data from epidemiological studies, but are derived only from the conclusion of one clinical study. 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, 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-based studies are prevented from making a more definite conclusion because they assessed retinal microvascular findings in other populations to assess the role of retinal photography in the measurement of stroke risk.

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Mild hypertensive retinopathy (retinal arteriolar signs only)</th>
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<tbody>
<tr>
<td>Sign</td>
<td>Diagnosis</td>
</tr>
<tr>
<td>Generalised arteriolar narrowing</td>
<td>• Qualitative examination of retinal photographs</td>
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<tr>
<td></td>
<td>• Risk of stroke (relative risk, 1.24; CI 95% 0.66 to 2.31)</td>
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<tr>
<td>Focal arteriolar narrowing</td>
<td>• Constricted area of two thirds or less of proximal and distal vessel segments</td>
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<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; EDTRS standard photograph</td>
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<table>
<thead>
<tr>
<th>Table 5</th>
<th>Moderate hypertensive retinopathy</th>
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<tbody>
<tr>
<td>Sign</td>
<td>Diagnosis</td>
</tr>
<tr>
<td>Microaneurysm</td>
<td>Present v absent</td>
</tr>
<tr>
<td>Retinal haemorrhage (dot, blot, or flame, shaped)</td>
<td>• Blot • Flame shaped • Both</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Soft exudates</td>
<td>Present v absent</td>
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</tbody>
</table>
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. 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.

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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