

Hypertensive retinopathy signs as risk indicators of cardiovascular morbidity and mortality

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Hypertensive retinopathy has long been regarded as a risk indicator for systemic morbidity and mortality. New population-based studies show that hypertensive retinopathy signs are strongly associated with blood pressure, but inconsistently associated with cholesterol and other risk factors of atherosclerosis. Mild hypertensive retinopathy signs, such as generalized and focal retinal arteriolar narrowing and arteriovenous nicking, are weakly associated with systemic vascular diseases. Moderate hypertensive retinopathy signs, such as isolated microaneurysms, haemorrhages and cotton-wool spots, are strongly associated with subclinical cerebrovascular disease and predict incident clinical stroke, congestive heart failure and cardiovascular mortality, independent of blood pressure and other traditional risk factors. These data support the concept that an assessment of retinal vascular changes may provide further information for vascular risk stratification in persons with hypertension.

Introduction

The retinal circulation undergoes a series of pathophysiological changes in response to elevated blood pressure.¹ These changes are manifested clinically as a spectrum of signs commonly referred to as hypertensive retinopathy.² Hypertensive retinal vascular signs can be broadly classified into arteriolar changes (generalized arteriolar narrowing, focal arteriolar narrowing, arteriovenous nicking and arteriolar wall opacification) and more advanced retinopathy lesions (microaneurysms, blot and flame-shaped haemorrhages, cotton-wool spots, hard exudates and optic disk swelling). With the exception of disk swelling, these signs can be detected fairly frequently in adult populations, even in persons without a known history of hypertension.³

The significance of hypertensive retinopathy signs as risk indicators of systemic morbidity and mortality has long been recognized since their description in patients with renal and cerebrovascular disease by

Accepted: July 13, 2005

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Marcus Gunn in the late nineteenth century.^{4,5} In fact, an assessment of hypertensive retinopathy signs for risk stratification is supported by international hypertension management guidelines, including the US Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC) and the British Society of Hypertension.^{6,7} The guidelines emphasize that hypertensive retinopathy, together with left ventricular hypertrophy and renal impairment, may be considered an indicator of target organ damage, suggesting that physicians should consider a more aggressive approach in managing these patients.⁷

Classification and diagnosis

The traditional classification of hypertensive retinopathy, dating back to 1939, was based on work by Keith *et al.*⁸ Although the modern classification system bears their name, the original paper⁸ was not an attempt to classify hypertensive retinopathy signs but to show that severity of hypertension itself was predictive of mortality. This classification and its modifications typically consist of four grades of hypertensive retinopathy with increasing severity: grade 1 consists of 'mild' generalized retinal arteriolar narrowing; grade 2 consists of 'more severe' generalized narrowing, focal areas of arteriolar narrowing and arteriovenous (AV) nicking; grade 3 consists of grade 1 and 2 signs plus the presence of retinal haemorrhages, microaneurysms, hard exudates and cotton-wool spots; grade 4, which is sometimes referred to as accelerated (malignant) hypertensive retinopathy, consists of signs in the preceding three grades plus optic disk swelling and macular oedema. Whereas the 3 year survival of persons with grade 1 hypertensive retinopathy was 70%, the survival was only 6% in those with grade 4 retinopathy.⁸ The major limitation of this classification system is the difficulty in distinguishing early hypertensive retinopathy severity (i.e. grade 1 from grade 2), and several proposals for a new systems have been made.^{2,3,9} A simple three-grade classification is proposed at the end of this article

It is important for the physician to be aware that some of these signs, particularly microaneurysms, haemorrhages and cotton-wool spots, may also be found in other systemic and ocular conditions (Table 1). The presence of hard exudates, for example, is more typical of diabetic retinopathy, while unilateral retinal signs may indicate carotid artery disease. Visual loss is suggestive of retinal vein occlusion, diabetic retinopathy, accelerated hypertension and other retinal diseases. Thus, in atypical scenarios, appropriate investigations may be necessary to exclude these important diseases.

Table 1 Differential diagnoses of isolated retinal haemorrhage, cotton-wool spots and microaneurysms

Systemic	Hypertension ^a Diabetes Carotid artery occlusion and ocular ischaemic syndrome Haematological disorders (e.g. anaemia, leukaemia, polycythaemia) ^a Inflammatory diseases (e.g. retinal vasculitis, Behcet's disease) ^a Systemic infectious diseases (e.g. HIV angiopathy, cytomegalovirus retinitis) ^a Radiation retinopathy
Ocular	Branch and central retinal vein occlusion Retinal telangiectasia

^aRetinal signs are usually seen in both eyes

Epidemiology

Recent population-based studies have provided data on the prevalence of various hypertensive retinopathy signs in the general population.^{10–17} Data from these studies indicates that hypertensive retinopathy signs, defined from retinal photographs, are seen in 3–14% of adult individuals aged ≥ 40 years (Fig. 1).

There are fewer studies of the long-term incidence of new hypertensive retinopathy signs.¹⁰ Data from the Beaver Dam Eye Study, a study of 4926 adults aged 43–86 years in Wisconsin, showed that the 5 year incidence of focal arteriolar narrowing, AV nicking, retinal haemorrhages and microaneurysms in people without diabetes ranged from 6% to 10%.¹⁰

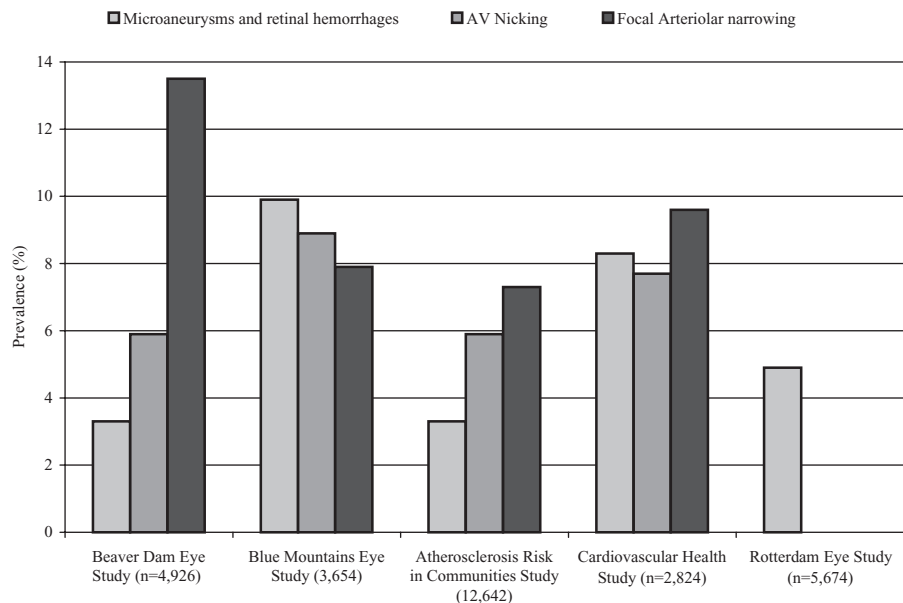


Fig. 1 Prevalence of hypertensive retinopathy: signs and selected population studies.

Associations with morbidity and mortality

Blood pressure

An abundance of data from clinical and population-based studies show a strong, graded and consistent association of hypertensive retinopathy signs with blood pressure (Table 2).^{10–13,15–17} Both the presence¹¹ and the development of new hypertensive retinopathy signs¹⁰ are strongly related to elevated blood pressure. In the Beaver Dam Eye Study, hypertensive individuals were 50–70% more likely to have retinal haemorrhages and microaneurysms, 30–40% more likely to have focal arteriolar narrowing and 70–80% more likely to have AV nicking than normotensive people. In addition, hypertensive persons whose blood pressure was still elevated despite use of antihypertensive medications, an indication of ‘poorer’ control, were more likely to develop retinopathy than individuals whose blood pressure was controlled with medication.

Several recent population-based studies have used standardized retinal photography methods to define hypertensive retinopathy signs and computer-based imaging methods to measure retinal arteriolar diameters from photographs. One of these is the Atherosclerosis Risk in Communities (ARIC) study, a population-based cohort investigation of cardiovascular disease of persons aged 45–64 years selected from four US communities. Retinal photography was added as a component of the examination and graded for the presence and severity of hypertensive retinal microvascular changes. The ARIC study demonstrated that generalized retinal arteriolar narrowing, indicated by narrower arteriolar diameters determined from photographs, was strongly associated with elevated blood pressure, a finding now confirmed in five other populations using similar methods.^{18–22} However, the clinical applicability of these findings is unclear, as the subtle degree of arteriolar narrowing associated with elevated blood pressure is difficult to estimate from ophthalmoscopy. For example, each 10 mmHg increase in mean arterial blood pressure was associated with a reduction of only 6 μm (3%) reduction in retinal arteriolar diameters in one study.²²

Data from ARIC and other studies provides increasing evidence that the pattern of associations of blood pressure with specific hypertensive retinopathy signs varies. Generalized retinal arteriolar narrowing and AV nicking appear to be markers of cumulative long-term hypertension damage, and are independently linked with past blood pressure levels measured 5–8 years before the retinal assessment.^{20,21,23} In contrast, focal arteriolar narrowing, retinal haemorrhages, microaneurysms and cotton-wool spots reflect more transient changes of acute blood pressure elevation, and are linked only with concurrent blood pressure measured at the time of the retinal assessment.^{20,21}

Table 2 Systemic associations of hypertensive retinopathy signs: selected population-based studies

Systemic associations	Haemorrhage	Microaneurysm	Cotton-wool spot	AV nicking	Focal arteriolar narrowing	General arteriolar narrowing	References
Current blood pressure	+++	+++	+++	+++	+++	+++	10, 13, 15, 17, 19–22, 49
Past blood pressure				+++		+++	20, 21
Carotid artery disease	+++	+++	+++	++		++	12, 16, 18
Clinical stroke	+++	+++	+++	++		+	30, 32
Subclinical cerebral disease	+++	+++	+++	++			30, 33
Cognitive impairment	+++	+++	+++				31
Coronary heart disease	+	+	+			++	36, 37
Congestive heart failure	+++	+++	+++	+	+	+	38
Incident hypertension					++	++	36, 37, 40–42
Incident diabetes	+++	+++	+++			++	50
Renal dysfunction	+++	+++	+++	+			26, 39
Cardiovascular mortality	+++	+++	+++			+	29
Inflammation	+	+	+	+		+	12, 18
Metabolic syndrome			+	+	+	+	51, 52

+++ Strong association (relative risks/odds ratios >2.0); ++ moderate association (relative risks/odds ratios 1.5–2.0), + weak association (relative risks/odds ratios <1.5)

An important finding in the Beaver Dam Eye Study was the observation that the association between blood pressure and retinal microvascular signs appears to be weaker with age,²² possibly reflecting greater sclerosis of retinal arterioles in older persons.

Atherosclerosis risk factors

In contrast with its strong association with blood pressure, hypertensive retinopathy signs have not been consistently linked to either direct measures of atherosclerosis, such as carotid artery stenosis, or atherosclerosis risk factors, such as hyperlipidaemia (Table 2). In the ARIC study, while controlling for blood pressure, generalized arteriolar narrowing was associated with carotid artery plaque but not stenosis, AV nicking was associated with carotid artery stenosis but not plaque and focal arteriolar narrowing was not related to either carotid artery measure.¹²

In the Hoorn Study in The Netherlands hyperglycaemia and abdominal obesity were independently related to incidence of retinal haemorrhages, microaneurysms, hard exudates and cotton-wool spots in the non-diabetic general population.²⁴ In the ARIC study, hypertensive retinopathy signs were related to larger waist circumference, an indicator of abdominal obesity.²⁵ However, not all studies have found associations between hypertensive retinopathy signs and abdominal obesity or dyslipidaemia.¹⁸

The association of hypertensive retinopathy signs with novel atherosclerosis risk factors has also been investigated. Cross-sectional associations of retinal arteriolar narrowing and AV nicking with biomarkers of inflammation (e.g. white blood cell counts) and endothelial dysfunction (e.g. von Willebrand factor) have been reported in the ARIC study¹² and by other groups.¹⁸

These studies emphasize the fact that typical signs of hypertensive retinopathy may be related to vascular processes other than blood pressure.

Stroke and cerebrovascular disease

Numerous studies have reported a strong association between various hypertensive retinopathy signs and both subclinical and clinical cerebrovascular disease²⁶⁻²⁸ and stroke mortality.²⁹ In the ARIC study, individuals with retinal haemorrhages, microaneurysms and cotton-wool spots, as defined from photographs, were two to four times more likely to develop an incident clinical stroke within 3 years, even when controlling for the effects of blood pressure, cigarette smoking, lipids and other risk factors.³⁰ Among the participants without stroke or

transient ischaemic attack, hypertensive retinopathy signs were also related to changes in cognitive function, as defined by standardized neuropsychological tests over a 6 year period,³¹ and to cerebral white matter hyperintensity lesions³² and atrophy, as defined from MRI scans.³³

One of the key observations was that the presence of hypertensive retinopathy may offer additional predictive value of clinical stroke risk in individuals with MRI-defined subclinical cerebral disease. In the ARIC study, individuals with both MRI-defined white matter lesions and hypertensive retinopathy were 18 times more likely [relative risk (RR) 18.1; 95% confidence interval (CI) 5.9–55.4] to develop an incident clinical stroke event than those without either white matter lesions or hypertensive retinopathy.³²

Coronary heart disease and heart failure

Hypertensive retinopathy signs have been linked with both subclinical and clinical coronary heart disease and congestive heart failure. For example, various hypertensive retinopathy signs have been associated with ischaemic changes on electrocardiogram,³⁴ severity of coronary artery stenosis on angiography³⁵ and incident coronary heart disease and myocardial infarction in men³⁶ and women.³⁷

The ARIC study reported that, after controlling for pre-existing risk factors, individuals with retinal haemorrhages, microaneurysms and cotton-wool spots were twice as likely (RR 1.96; 95% CI 1.52–2.56) to develop congestive heart failure as individuals without retinopathy.³⁸ In fact, among low-risk individuals (without pre-existing heart disease, diabetes or hypertension), the presence of hypertensive retinopathy signs predicted a 3-fold increased risk of heart failure events (RR 2.97, 95% CI 1.49–5.91). This is compatible with the interpretation that microvascular damage to the myocardium from hypertension and other systemic processes may be a contributing factor in the development of heart failure.

Other systemic diseases

A number of systemic diseases have been associated with different hypertensive retinopathy signs (Table 2). In the ARIC study, individuals with AV nicking, retinal haemorrhages, microaneurysms and cotton-wool spots were more likely to develop renal dysfunction than those without these signs.³⁹ This association was independent of blood pressure, diabetes and other risk factors, and was also seen in persons without diabetes or hypertension.

Data from three population-based studies suggest that generalized retinal arteriolar narrowing, a marker of blood pressure damage, may in fact predict the development of incident hypertension.^{40–42} The ARIC study showed that normotensive participants who had generalized arteriolar narrowing were 60% more likely to be diagnosed with hypertension within a subsequent 3-year period than normotensive individuals without arteriolar narrowing (RR 1.62; 95% CI 1.21–2.18).⁴¹ This association was independent of an individual's pre-existing blood pressure levels, body mass index and other known hypertension risk factors.

The ARIC and Beaver Dam Eye Studies have also shown that generalized retinal arteriolar narrowing predicts the incidence of type 2 diabetes among persons initially free of diabetes, independent of diabetes risk factors.^{43,44} Thus generalized arteriolar narrowing, possibly reflecting various systemic peripheral arteriolar changes, may be a preclinical marker of overt hypertension and diabetes.

Cardiovascular mortality

The study by Keith *et al.*⁸ was amongst the first to show a dose-dependent increase in mortality with severity of hypertensive retinopathy changes. Since then, numerous studies conducted in the 1950s and 1960s have further shown that persons with hypertension and retinopathy signs are at increased risk of mortality.^{34,45–47} However, inferences from many older studies are limited because of the subjective evaluation of hypertensive retinopathy signs, the lack of data on cause-specific mortality rates and inadequate control for potential confounders such as blood pressure and diabetes.

Nonetheless, more recent studies have provided stronger evidence that hypertensive signs are markers of mortality risk. In a nested case-control analysis of the Beaver Dam Eye Study, individuals with retinal microaneurysms and retinal haemorrhages were twice as likely to die from cardiovascular events as those without these signs.²⁹

Clinical applications

Data from recent studies support the current hypertension guidelines regarding the prognostic significance of retinopathy signs.^{6,7} The information obtained from an assessment of the retinopathy status appears to be independent of, and qualitatively different from, that of measuring blood pressure or serum lipids, as the presence of retinopathy signs indicates susceptibility and the onset of preclinical systemic vascular disease. In particular, it seems that individuals with certain hypertensive

retinopathy signs (e.g. retinal haemorrhages, microaneurysms and cotton-wool spots) should be more closely monitored for cardiovascular risk, and may benefit from further investigations (e.g. echocardiogram for heart function) if clinically indicated.

A three-grade classification system for hypertensive retinopathy is shown in Table 3, and a suggested approach for patients with various hypertensive retinopathy grades is shown in Figure 2. It is important to emphasize that the management for patients with hypertension and cardiovascular disease should continue to follow standard risk prediction approaches (i.e. based on assessment of age and gender of the patient, blood pressure and lipid levels, cigarette smoking status etc).

The classification in Table 3 groups hypertensive retinopathy signs into mild, moderate and accelerated (malignant). Patients with mild hypertensive retinopathy signs (Figure 3A) will probably require routine

Table 3 Classification of hypertensive retinopathy

Retinopathy	Description	Systemic associations
Mild	One or more of the following signs: generalized arteriolar narrowing, focal arteriolar narrowing, AV nicking, arteriolar wall opacity (silver-wiring)	Weak associations with stroke, coronary heart disease and cardiovascular mortality
Moderate	Mild retinopathy with one or more of the following signs: retinal haemorrhages (blot, dot or flame-shaped), microaneurysms, cotton-wool spot, hard exudates	Strong association with stroke, congestive heart failure, renal dysfunction and cardiovascular mortality
Accelerated	Moderate retinopathy signs plus optic disk swelling; may be associated with visual loss	Associated with mortality and renal failure

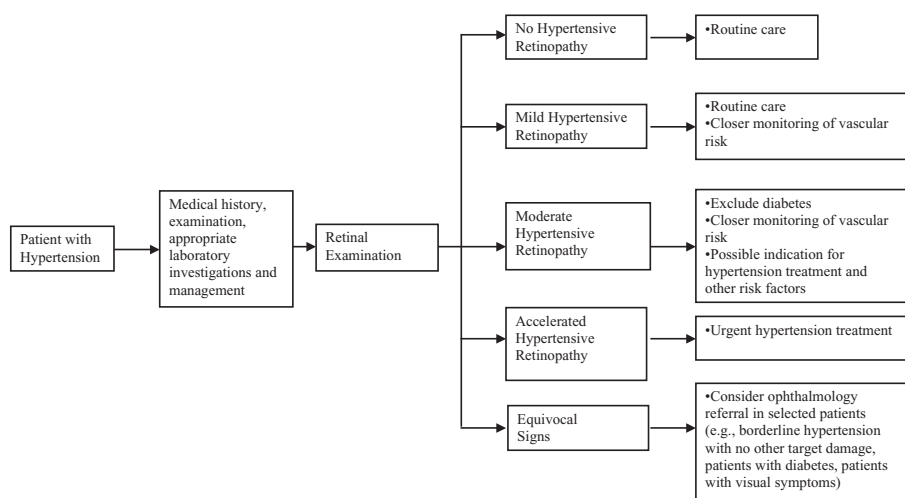


Fig. 2 Evaluation and management of a patient with hypertensive retinopathy.

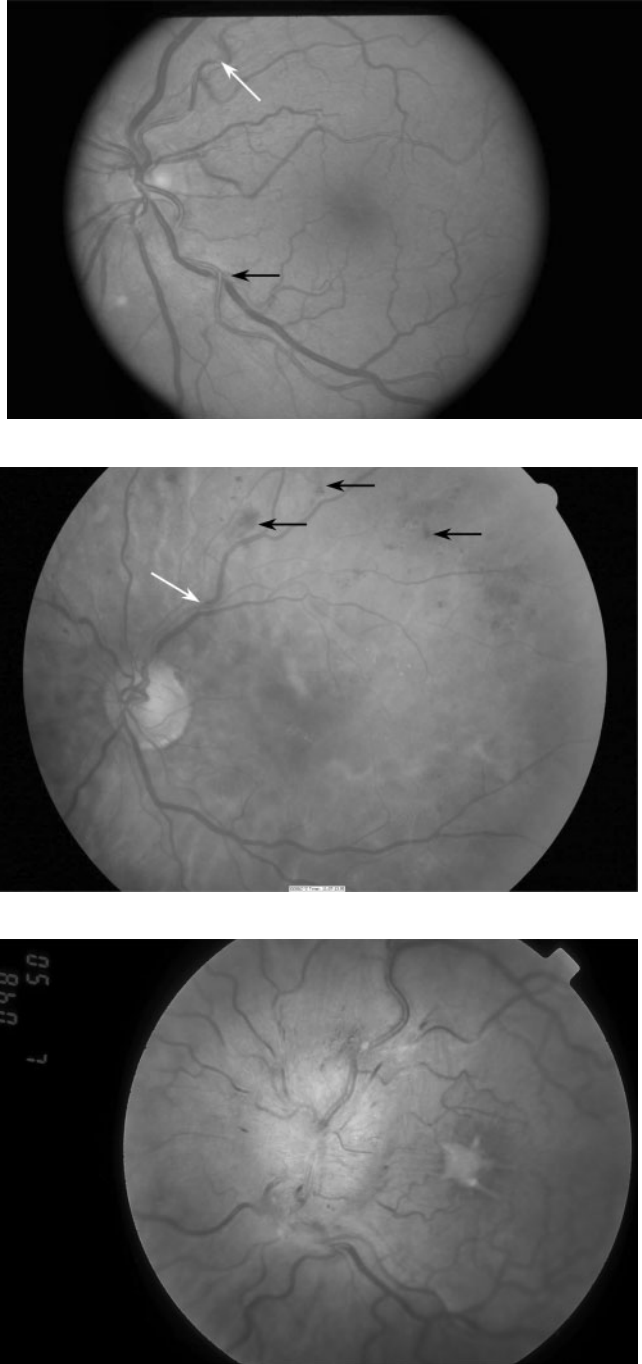


Fig. 3 (A) Mild hypertensive retinopathy: AV nicking (black arrow) and focal narrowing (white arrow). (B) Moderate hypertensive retinopathy: retinal haemorrhages (black arrows), AV nicking (white arrow) and generalized retinal arteriolar narrowing. (C) Accelerated (malignant) retinopathy: swelling of optic disk, retinal haemorrhages and cotton-wool spots.

care, and blood pressure control should be based on established guidelines.^{6,7} Patients with moderate hypertensive retinopathy signs (retinal haemorrhage, microaneurysm, cotton-wool spots) (Fig. 3B) may benefit from further assessment of vascular risk (e.g. assessment of cholesterol levels) and, if clinically indicated, appropriate risk reduction therapy (e.g. cholesterol-lowering agents). Patients with accelerated hypertensive retinopathy (bilateral disk swelling in the presence of moderate hypertensive retinopathy) (Figure 3C), which is relatively rare in the general population but may occur in conjunction with severe hypertension, will continue to need urgent immediate antihypertensive management, including possible administration of intravenous medication. In such scenarios, physicians should aim for a small stepwise control of blood pressure over a few hours, and avoid a sudden reduction in blood pressure which may lead to stroke.

There have been several experimental studies^{48,49} and clinical reports⁵⁰⁻⁵² of regression of hypertensive retinopathy signs with control of blood pressure. With adequate hypertension treatment, resolution of hypertensive retinopathy signs may occur over a period of 6 months⁵² to a year.⁵¹ Thus follow-up of patients for up to a year after diagnosis may be needed.

These studies also provide some evidence that specifically targeting the microcirculation in hypertensive individuals may further reduce cardiovascular morbidity and mortality. For example, certain antihypertensive agents (e.g. ACE inhibitors) have been suggested to have direct beneficial effects on microvessel structure and function, beyond their primary effect on lowering blood pressure.⁵² Therefore such agents may have added therapeutic value in preventing and treating cardiovascular diseases. However, whether these specific therapies may reverse or reduce retinopathy changes, and whether this will result in reduced cardiovascular risk, is currently unclear.

Conclusions

Hypertensive retinopathy signs may differ in their associations with systemic diseases. Isolated retinal haemorrhages, microaneurysms and cotton-wool spots (moderate hypertensive retinopathy) appear to be associated with risk of subclinical and clinical stroke, other cerebrovascular outcomes, congestive heart failure and cardiovascular mortality, independent of traditional risk factors. In contrast, the systemic associations for generalized retinal arteriolar narrowing, focal arteriolar narrowing and AV nicking (mild hypertensive retinopathy) appear to be weaker and less consistent. An assessment of hypertensive retinopathy signs may provide important information for vascular risk stratification

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