HYPERTENSIVE RETINOPATHY

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CHAPTER CONTENTS

AIMS

This unit aims to outline the diagnosis and management of hypertensive retinopathy via developing:

- A protocol for assessing the signs of hypertensive retinopathy
- A framework for making a differential diagnosis of hypertensive retinopathy
- Management guidelines for hypertensive retinopathy

LEARNING OUTCOMES

After completing this unit, tha student should be able to:

- Understand the diversity of presentations of hypertensive retinopathy
- Appreciate the complex nature of the aetiology of hypertensive retinopathy
- Develop a plan for clinical investigation of these conditions
- Understand that the treatment options are complex

INTRODUCTION

Hypertension is classified as either primary (essential) hypertension or secondary hypertension. In approximately 90–95% of cases the categorization is primary hypertension which means high blood pressure with no obvious underlying medical cause. The remaining 5–10% of cases categorized as secondary hypertension are caused by other conditions that affect e.g. the kidneys, arteries, heart or endocrine system.

Retinal vascular changes occur when there is chronically elevated systemic arterial hypertension where the blood pressure is greater than 140/90 mmHg. These changes usually present in people aged 50 to 60 years or older. Those with hypertension are often asymptomatic in the early course of the disease.

It is important to be aware that hypertensive retinal changes can be seen in young people.

Complications associated with hypertension include:

- Increased risk of arteriosclerosis
- Ventricular hypertrophy and failure
- Renal disease
- Retinal vein occlusion
- Non-arteritic anterior ischaemic optic neuropathy (NAION)
- Cranial nerve palsies (CN III, IV, VI, VII)
- Diabetic retinopathy

REVIEW OF BLOOD PRESSURE

The measure of blood pressure is made up of two components.

Systolic: is the blood pressure when the heart beats while pumping blood.

Diastolic: is the blood pressure when the heart is at rest between beats.

Category	Systolic (mmHg)		Diastolic (mmHg)
Normal	< 120	*And*	< 80
Pre-hypertension	120–139	*Or*	80–89

Stage 1 hypertension	140–159	*Or*	90–99
Stage 2 hypertension	160 - 179	*Or*	100 or 110
Hypertensive crisis /malignant hypertension	> 180		> 120

Table 1: *Classification of blood pressure*

HIGH BLOOD PRESSURE (SYSTEMIC)

It is estimated that approximately 25% of the population have hypertension which rises to 60% of those aged 60 years or older. Typically, the condition is asymptomatic until the later, chronic stage.

High blood pressure can lead to e.g. atherosclerosis, cardiac hypertrophy, heart failure, etc.

The main risk factors include:

- Age
- Diabetes
- Ethnicity (e.g. African American)
- Lack of physical activity

The main factors that affect and regulate systemic blood pressure include:

- Heart rate/'pumping power'
- Blood volume
- Vessel resistance (vessel size, elasticity, 'roughness')
- Blood viscosity ('thick' vs 'thin'; effect of increased clotting)
- Kidney 'integrity' (angiotensin/renin system)

Other factors include:

- Other systemic conditions
- Ethnicity
- Diet (especially sodium intake)

PATHOPHYSIOLOGICAL CHANGES IN HYPERTENSIVE OCULAR DISEASE

Hypertensive retinopathy is a common clinical presentation that may include observations such as:

- Vasoconstriction, sclerosis and exudative phase
- Complications of the sclerotic phase

Hypertension can affect the choroid and cause pathological changes.

Observations of hypertensive optic neuropathy include:

- Optic disc oedema
- Optic atrophy
- Ischaemic optic neuropathy

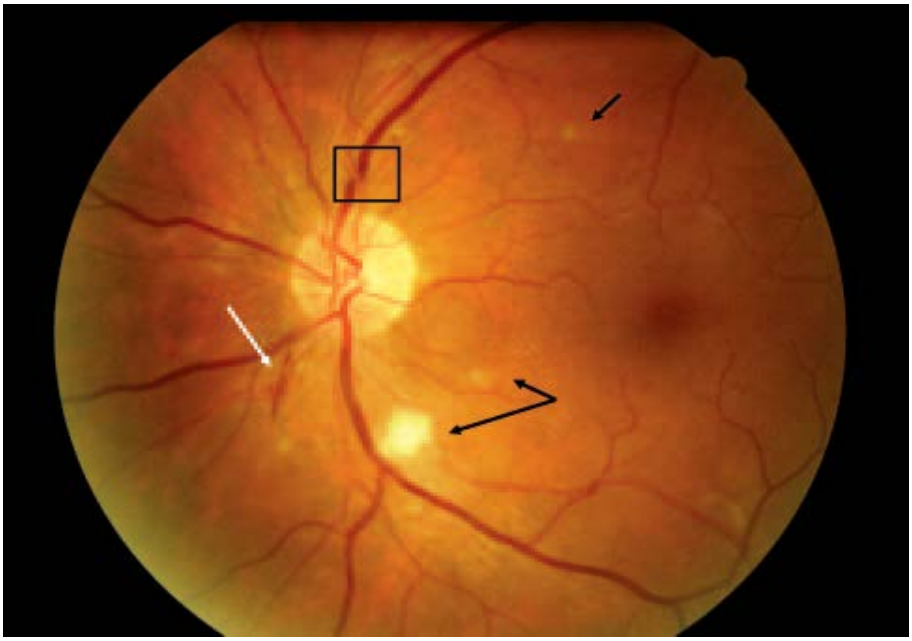


Figure 1: *Hypertensive retinopathy signs - arteriovenous nicking (box), cotton wool spots (black arrows), and retinal haemorrhage (white arrow). (Stroke, 2008)*

HYPERTENSIVE RETINOPATHY

There are usually no symptoms in the majority of people who have hypertensive retinopathy.

The presence of hypertension may be suspected on the observation of changes to the ocular fundus.

Signs (arteriosclerosis): usually bilateral

- Broadening of arteriolar light reflex
- Vessel walls are thickened
- AV nicking at arterio-venous crossing points
    - Thickened/less pliant arteries indent and displace more pliant veins
- Venous dilatation or banking distal to an AV crossing
- Focal constriction and dilatation of arterioles
- Venous obstruction
- Increased arteriolar tortuosity
- Retinal neovascularization
- Retinal emboli
- Copper wiring (mild cases)
- Silver wiring (advanced cases)
- Vascular leakage
- Cotton-wool spots
    - Focal retinal ischemia

WHAT IS AV "NICKING"?

- Retinal vein is less apparent (mild cases) and/or disappears (severe cases) on either side of the artery
- Arteriovenous (AV) nicking is indicative of mild hypertension

AV CROSSING AND VESSEL CHANGES

There are many vessel changes that occur in hypertensive retinopathy including:

- Banking of the venule distal to crossing (Bonnet's sign)
- Nipping of the blood column (Gunn's sign)
- Displacement of the venule at right angles to arteriole (Salus' sign)
- "Copper wire" artery (blood flow restricted due to artery wall changes)
- "Silver wire" artery (vessel wall becomes opaque and blood column not seen (hyalinised), central light reflex occupies width of the arteriole, appears as a "silver wire")

COTTON-WOOL SPOTS

Cotton-wool spots (CWS) are a result of occlusion of the retinal pre-capillary arterioles supplying the nerve fiber layer (NFL). They appear as white, fluffy lesions in the NFL and, as a result, are inaccurately termed as a "soft exudate".

The lesions are sometimes called a NFL infarction.

The CWS are associated with interruption to the axoplasmic flow in the nerve axons which results in localized nerve swelling.

HYPERTENSIVE RETINOPATHY SIGNS – EXUDATIVE PHASE

Some signs that may be observed in the exudative phase of hypertensive retinopathy include:

- Retinal oedema
- Flame-shaped haemorrhages
- Blot haemorrhages
- Hard exudates
- Microaneurysms

HARD EXUDATE (INTRA-RETINAL LIPID EXUDATE)

Exudate is an accumulation of lipids that leak from the retinal capillaries and microaneurysms. They may form in a circinate pattern ("macula star").

What are the clinical signs in acute hypertensive retinopathy and in chronic hypertensive retinopathy?

MALIGNANT HYPERTENSIVE RETINOPATHY

This is a rare syndrome where there is a rapid and severe elevation of blood pressure to greater than 200/140 mmHg.

The average age at diagnosis is 40 years and it occurs more in men than women. About 1% of hypertensive patients develop malignant hypertension. Most patients have pre-existing primary or secondary hypertension.

The presence of systemic findings defines malignant hypertension (including ocular, cardiac, renal and cerebral injury). Retinal, choroidal and optic nerve changes occur secondary to acutely elevated systemic arterial blood pressure >200/140mmHg.

A persistently elevated malignant hypertension can lead to a rapidly fatal course, with heart failure, myocardial infarction, stroke, or renal failure.

Malignant hypertension rarely occurs in individuals receiving treatment for hypertension. With effective anti-hypertensive treatment, nearly 50% of patients survive greater than 5 years.

- Common symptoms
  - Headaches, diplopia, dimness of vision, scotoma, photopsia
- Key features
  - Retinal arteriolar spasm, vascular leakage, optic disc oedema, superficial retinal haemorrhages, cotton-wool spots (typically resolve in 3-6 weeks), NFL loss, serous retinal detachment

- Associated features
  - Choroidal ischaemia, RPE changes, hypertensive optic neuropathy, cortical blindness.
- Systemic features
  - Proteinuria, stroke, kidney failure, encephalopathy

Signs associated with severe hypertensive retinopathy include:

- Vascular changes
- Disc oedema with blurring of the disc borders
- Haemorrhages
- Exudates

ACUTE "MALIGNANT" HYPERTENSIVE RETINOPATHY

Key features of the condition include:

- Macular star (hard exudates)
- Optic disc swelling (bilateral, referred as papilloedema)
- It is an ocular emergency with poor prognosis
- Needs referral for immediate hospitalisation

HYPERTENSIVE RETINOPATHY CLASSIFICATION SCHEMES

Several classification schemes are used to mark the stages of hypertensive retinal changes.

A. Keith-Wagener-Barker classification: combines clinical findings of hypertension and atherosclerosis
B. Modified Scheie classification

All the schemes used have some limitations including:

- Classification is difficult because of variable clinical findings
- Difficult to distinguish low grade retinopathy

As a result no one scheme is universally adopted. An accurate description of ocular findings and history remains the most valuable "classification system".

KEITH-WAGENER-BARKER CLASSIFICATION

Group 1	Mild to moderate narrowing or sclerosis of arterioles; AV ratio is 1:2 Silver wire appearance of the vessel
Group 2	Moderate to marked narrowing of the arterioles; AV ratio is <1:2 Local and/or generalized narrowing of arterioles Exaggeration of the light reflex Arteriovenous crossing changes
Group 3	Retinal arteriolar narrowing and focal constriction Retinal oedema Cotton-wool patches Haemorrhages
Group 4	As for Group 3, plus 'papilloedema + macula star'

Table 2: *Keith-Wagener-Barker classification*

MODIFIED SCHEIE CLASSIFICATION

Grade 0	No changes/normal
Grade 1	Minimal arteriolar narrowing; barely detectable light reflex changes
Grade 2	Obvious arteriolar narrowing with focal irregularities; obvious increased light reflex changes, deflection of veins at A/V crossings (Salus' sign)
Grade 3	Grade 2 + retinal haemorrhages and/or exudate; copper-wire arterioles; tapering of veins both sides of A/V crossings (Gunn's sign), right angle deflection of veins
Grade 4	Grade 3; silver-wire arterioles + swollen optic nerve (Malignant hypertension)

Table 3: *Modified Scheie classification*

ANOTHER SIMPLIFIED CLASSIFICATION SYSTEM

CLASSIFICATION ON THE BASIS OF RECENT POPULATION-BASED DATA.

Grade of Retinopathy	Retinal Signs	Systemic Associations
None	No detectable signs	None
Mild	Generalized arteriolar narrowing, focal arteriolar narrowing, arteriovenous nicking, opacity ("copper wiring") of arteriolar wall, or a combination of these signs	Modest association with risk of clinical stroke, subclinical stroke, coronary heart disease, and death
Moderate	Hemorrhage (blot, dot, or flame-shaped), microaneurysm, cotton-wool spot, hard exudate, or a combination of these signs	Strong association with risk of clinical stroke, subclinical stroke, cognitive decline, and death from cardiovascular causes
Malignant	Signs of moderate retinopathy plus swelling of the optic disc	Strong association with death

Table 4: *Classification of Hypertensive Retinopathy on the Basis of Recent Population-Based Data.*

A modest association is defined as an odds ratio of greater than 1 but less than 2. A strong association is defined as an odds ratio of 2 or greater.

Anterior ischemic optic neuropathy, characterized by unilateral swelling of the optic disc, visual loss and sectorial visual-field loss, should be ruled out.

Classification of retinal microvascular signs

Grade of Retinopathy	Retinal Signs	Systemic Associations*	Suggested management
None	No detectable signs	None	
Mild	Generalized arteriolar narrowing, focal arteriolar narrowing, arteriovenous nicking, arteriolar wall opacity (silver-wiring)	Moderate and weak associations with stroke, ischaemic heart disease, cardiovascular mortality	Routine care, closer monitoring of blood pressure, better control of blood pressure in persons with known hypertension
Moderate	Retinal haemorrhage (blot, dot or flame-shaped), microaneurysm, cotton-wool spot, hard exudates	Strong association with stroke, cognitive decline, congestive heart failure, renal dysfunction, and cardiovascular mortality	May require physician referral, need to exclude diabetes, possible indication for treatment of hypertension and other risk factors in persons without known hypertension, better control of blood pressure and risk factors in persons with known hypertension
Malignant	Moderate retinopathy signs plus optic disc swelling	Associated with mortality	Urgent treatment of hypertension

Table 5: *Classification of retinal microvascular signs*

Note that these grades do not imply a sequential temporal relationship of mild to moderate, and moderate to malignant.
Strength of association: relative risk/odds ratio >2.0 (Strong), 1.5-2.0 (Moderate), <1.5 (Weak).

Anterior ischaemic optic neuropathy, characterized by unilateral optic disc swelling, visual loss and sectoral visual field loss, should be excluded.

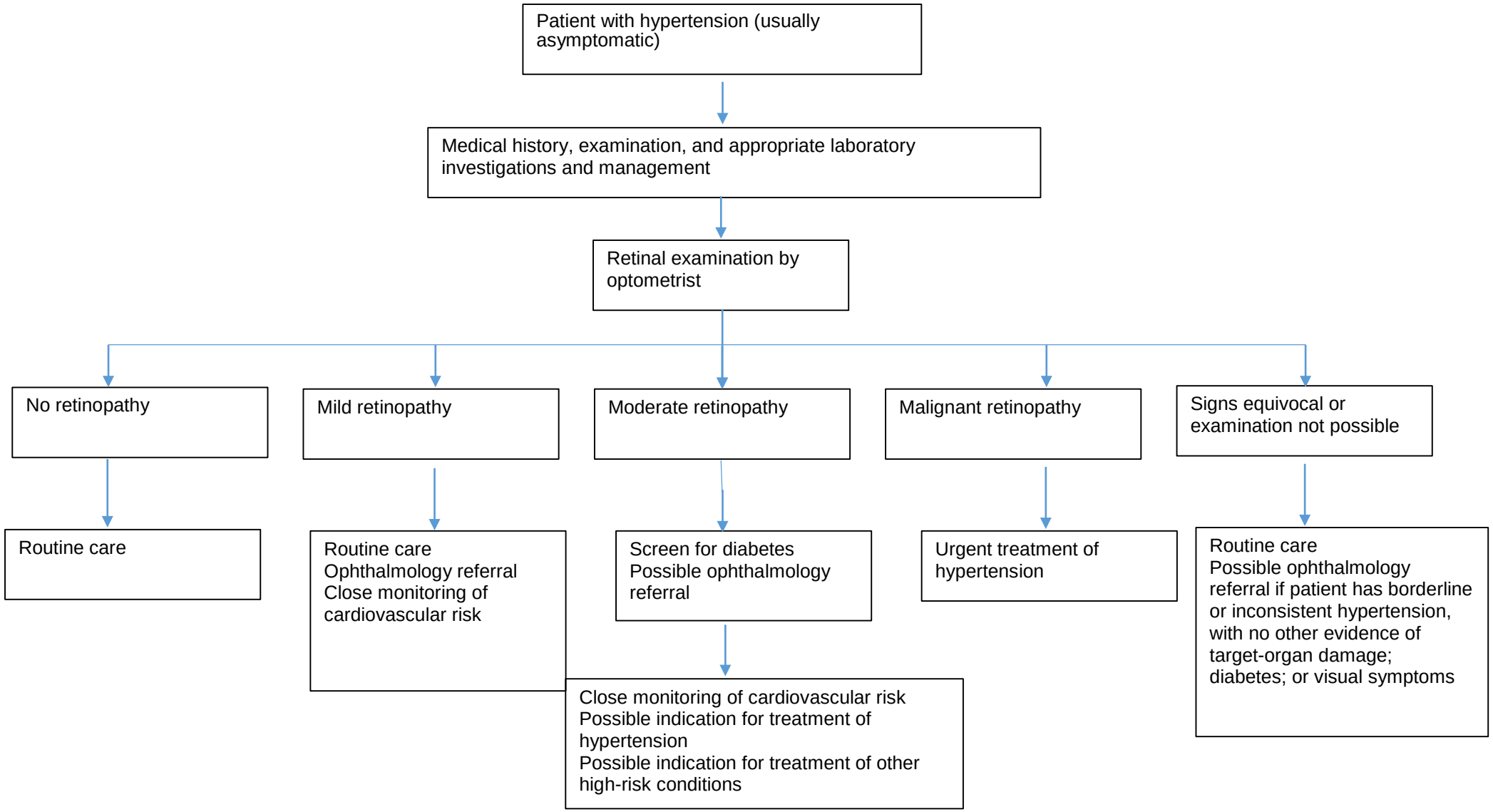
(Based on Blue Mountains Eye Study (BMES), Wong and Mitchell, 2004)

MANAGEMENT OF MALIGNANT HYPERTENSIVE RETINOPATHY

Optimised management of a person with hypertensive retinopathy involves consultation with the GP and other healthcare practitioners.

- Changes in lifestyle and medication can halt progress of retinal changes, but arteriolar narrowing and AV nicking are usually permanent
- Lowering of the BP in a controlled fashion can minimise end-organ damage.

***Figure 2**: Evaluation and management of hypertensive retinopathy (Wong & Mitchell, 2004)*



HYPERTENSIVE RETINOPATHY – A MARKER OF SYSTEMIC DISEASE

Epidemiological studies (Wong & Mitchell, 2004, Wong & Macintosh, 2005) indicate that generalised narrowing of the arterioles and AV nicking are markers of vascular disease from chronic hypertension.

Other signs such as cotton-wool spots, focal arteriolar narrowing, microaneurysms and haemorrhages are related to current hypertension.

- Strong association between signs of hypertensive retinopathy and risk of stroke (Baker et al., Stroke 2008); transient ischaemic attack and acute stroke (Wang et al., Stroke 2011)
- Generalised retinal arteriolar narrowing associated with coronary heart diseases
    - Potential early markers of pre-hypertensive state?

Retinal signs	Systemic associations	Strength*	Studies and references
Retinal haemorrhages	Current blood pressure	**Strong**	ARIC (Sharrett *et al.*, 1999), BMES (Wang *et al.*, 2003), BDES (Wong *et al.*, 2003a), CHS (Wong *et al.*, 2002a)
Microaneurysms	Carotid artery disease	**Strong**	ARIC (Klein *et al.*, 2000), CHS (Wong *et al.*, 2003c)
Cotton-wool spots	Incident clinical stroke	**Strong**	ARIC (Wong *et al.*, 2001a, 2002b), BMES (Mitchell *et al.*,
	Subclinical cerebral	**Strong**	ĀRĪC (Wong *et al.*, 2002b, 2003d)
	Cognitive impairment	**Strong**	ARIC (Wong *et al.*, 2002d)
	Renal dysfunction	**Strong**	ARIC (Wong *et al.*, 2004b)
	Cardiovascular mortality	**Strong**	BDES (Wong *et al.*, 2003b), BMES (Mitchell *et al.*, 2002)
Arteriovenous nicking	Current blood pressure	**Strong**	ARIC (Sharrett *et al.*, 1999), BMES (Wang *et al.*, 2003), BDES (Klein *et al.*, 1994; Klein, at al, 1997) CHS (Wong *et al.*, 2002a)
	Past blood pressure	**Strong**	ARIC (Sharrett *et al.*, 1999), CHS (Wong *et al.*, 2002a)
	Inflammatory markers	Weak	ARIC (Klein *et al.*, 1999)
	Endothelial dysfunction	Weak	ARIC (Klein *et al.*, 1999)
	Metabolic syndrome	Weak	ARIC (Wong *et al.*, 2004a), BMES (Leung *et al.*, 2005)
	Incident clinical stroke	Moderate	ARIC (Wong *et al.*, 2001a, 2002b), BMES (Mitchell *et al.*,
	Subclinical cerebral	Moderate	ĀRĪC (Wong *et al.*, 2002b)
	Renal dysfunction	Weak	ARIC (Wong *et al.*, 2004b)
Focal arteriolar	Current blood pressure	**Strong**	ARIC (Sharrett *et al.*, 1999), BMES (Wang *et al.*, 2003), BDES (Klein *et al.*, 1994, 1997), CHS (Wong *et al.*,
	Incident hypertension	Moderate	ARIC (Wong *et al.*, 2004c)
	Metabolic syndrome	Weak	ARIC (Wong *et al.*, 2004a)
Generalised arteriolar narrowing	Current blood pressure	**Strong**	ARIC (Sharrett *et al.*, 1999), BMES (Wang *et al.*, 2003), BDES (Klein *et al.*, 1994), CHS (Wong *et al.*, 2002a), Rotterdam (Ikram *et al.*, 2004)
	Past blood pressure	**Strong**	ARIC (Sharrett *et al.*, 1999), BMES (Leung *et al.*, 2004), CHS (Wong *et al.*, 2002a)
	Incident hypertension	Moderate	ARIC (Wong *et al.*, 2004c), BDES (Wong *et al.*, 2004e), BMES (Smith *et al.*, 2004)
	Inflammatory markers	Weak	ARIC (Klein *et al.*, 1999), Rotterdam (Ikram *et al.*, 2004)
	Carotid atherosclerosis	Moderate	ARIC (Klein *et al.*, 1999; Liao *et al.*, 2004), Rotterdam (Ikram *et al.*, 2004)
	Metabolic syndrome	Weak	ARIC (Wong *et al.*, 2004a), BMES (Leung *et al.*, 2005)
	Incident clinical stroke	Weak	ARIC (Wong *et al.*, 2001a, 2002b), BMES (Mitchell *et al.*,
	Incident heart disease	Moderate	ĀRĪC (Wong *et al.*, 2002c)
	Cardiovascular mortality	Weak	BDES (Wong *et al.*, 2003b)

*Strength of association: Relative risk/odds ratio >2.0 (Strong), 1.5 to 2.0 (Moderate), <1.5 (Weak).

***Table 6**: Systemic associations of retinal microvascular signs, selected population-based studies (Wong & Macintosh, 2005)*

HYPERTENSIVE RETINOPATHY OVERVIEW

The signs of hypertensive retinopathy are common and include:

- AV nicking (AV ratio) and generalised arteriole narrowing are associated with increased BP
- Vasoconstriction
- Some retinal signs (retinal haemorrhages, cotton-wool spots and microaneurysms) can predict stroke and death from stroke, independently of blood pressure

Patients with these signs require close monitoring. The degree and duration of hypertension are main factors in the severity of retinopathy. Associations with other systemic problems e.g. diabetes, can worsen retinopathy.

It is important to be aware of other systemic health problems the patient may have and to consult with their GP, etc.

HYPERTENSIVE CHOROIDOPATHY

This condition typically involves younger patients (e.g. toxaemia of pregnancy, connective tissue disease, renal disease) with accelerated malignant hypertension and no time for sclerotic long-term damage to vessels.

It is a rare condition that has a poor prognosis.

Signs of hypertensive choroidopathy include:

- Multiple choroidal infarcts
    - Elschnig spots which are ischaemic RPE infarcts that coincide with hypoperfusion of underlying choroid
- Hyperpigmented areas along choroidal arteries
    - Siegrist streaks which are ischemic infarcts at the equator and have a more linear appearance
- Exudative retinal detachment

HYPERTENSIVE OPTIC NEUROPATHY

This condition is associated with malignant hypertension. Signs of hypertensive optic neuropathy include:

- Optic nerve swelling
- Optic atrophy (a long term change)
- Ischaemic optic neuropathy