# The eye in hypertension

*Tien Wong, Paul Mitchell*

**Hypertension has a range of effects on the eye. Hypertensive retinopathy refers to retinal microvascular signs that develop in response to raised blood pressure. Signs of hypertensive retinopathy are frequently seen in adults 40 years and older, and are predictive of incident stroke, congestive heart failure, and cardiovascular mortality—independently of traditional risk factors. Hypertension is also a major risk factor for the development of other retinal vascular diseases, such as retinal vein and artery occlusion, and ischaemic optic neuropathy. High blood pressure increases the risk of both development of diabetic retinopathy and its progression. Adequate control of blood pressure has been proven in randomised clinical trials to reduce vision loss associated with diabetic retinopathy. Finally, hypertension has been implicated in the pathogenesis of glaucoma and age-related macular degeneration. Recognition of the ocular effects of blood pressure could allow physicians to better manage patients with hypertension, and to monitor its end-organ effects.**

*Lancet* 2007; 369: 425–35

**Centre for Eye Research Australia, University of Melbourne, Australia and Singapore Eye Research Institute, Yong Loo Lin School of Medicine, National University of Singapore** (T Y Wong FRCSE); and **Centre for Vision Research, University of Sydney, Australia** (P Mitchell FRANZCO)

Correspondence to:
Dr Tien Wong, University of Melbourne, 32 Gisborne Street, East Melbourne 3002, Australia
**twong@unimelb.edu.au**

Hypertension has profound effects on the structure and function of the eye. First, the retinal, choroidal, and optic nerve circulations undergo a series of pathophysiological changes in response to raised blood pressure, resulting in a range of clinical signs referred to as hypertensive retinopathy, hypertensive choroidopathy, and hypertensive optic neuropathy. Second, hypertension is an important risk factor for the development of potentially blinding vascular diseases of the eye, including retinal vein and artery occlusion, retinal–arteriolar emboli, and diabetic retinopathy. Finally, hypertension might be a pathogenic factor for non-vascular ocular diseases, including two of the leading causes of blindness—glaucoma and age-related macular degeneration. We summarise the links between hypertension and these disorders.

## Direct ocular effects of hypertension

Hypertensive retinopathy refers to retinal microvascular signs that are related to raised blood pressure.[1] The underlying pathophysiology of these signs can be divided into stages.[2] The initial response of the retinal circulation to a rise in blood pressure is vasospasm and an increase in vasomotor tone, which is seen clinically as generalised retinal–arteriolar narrowing. Subsequently, chronic arteriosclerotic changes, such as intimal thickening, media-wall hyperplasia, and hyaline degeneration, develop. These changes manifest as diffuse and focal areas of arteriolar narrowing, opacification of arteriolar walls (described as silver or copper wiring), and compression of the venules by arterioles at their common adventitial locations (termed arteriovenous nipping or nicking). With more pronounced high blood pressure, the blood–retinal barrier breaks down, resulting in exudation of blood (haemorrhages), lipids (hard exudates), and subsequent ischaemia of nerve-fibre layers (known as cotton-wool spots). In the setting of severely high blood pressure, raised intracranial pressure and concomitant optic nerve ischaemia can lead to disc swelling (papilloedema), which is sometimes referred to as severe or malignant hypertension or hypertensive optic neuropathy. Other mechanisms linking high blood pressure with signs of hypertensive retinopathy could include inflammation,[3] endothelial dysfunction,[3,4] and angiogenesis.[5]

Clinically, signs of hypertensive retinopathy are classified into four grades of increasing severity.[6] Although this system is widely used, early retinopathy grades are difficult to distinguish.[7] Further, the prognostic implications of early hypertensive retinopathy grades are unclear.[8] Thus, a three-grade classification system has been proposed.[8] In this system, mild retinopathy would be identified by retinal–arteriolar signs, such as generalised and focal arteriolar narrowing, arteriolar wall opacification, and arteriovenous nipping (figure 1A). In addition to these signs, moderate retinopathy would be recognised by flame-shaped or blot-shaped haemorrhages, cotton-wool spots, hard exudates, microaneurysms, or a combination of all of these factors. Severe retinopathy would display some or all of these retinopathy signs, as well as swelling of the optic disc (figure 1B).

Population-based studies[9–12] that used retinal photographs and standardised assessment methods to define signs of retinopathy detected signs of hypertensive retinopathy in 2–14% of the non-diabetic population aged 40 years and older. The investigators reported that these signs were strongly associated with high blood pressure.[9–12] One population-based study related both the prevalence,[9] and incidence,[13] of hypertensive retinopathy signs to raised blood pressure. Computer-imaging techniques have been used to show that high blood pressure is associated with narrower retinal–arteriolar diameters, but does not affect venular diameters.[14–17]

### Search strategy and selection criteria

We searched MEDLINE using PubMed with the search terms "systemic hypertension" and "blood pressure", in combination with "eye", "retinopathy", "retinal arteriolar disease", "arterio-venous nipping", "retinal vein occlusion", "retinal artery occlusion", "retinal emboli", "retinal macroaneurysm", "ischaemic optic neuropathy", "diabetes", "glaucoma", and "age-related macular degeneration". We largely selected publications in the past 5 years, but did not exclude older publications that are commonly referenced or highly regarded. We also searched the reference lists of articles identified by this search strategy and selected those we judged relevant. Review articles are also cited to provide readers with more details and references.

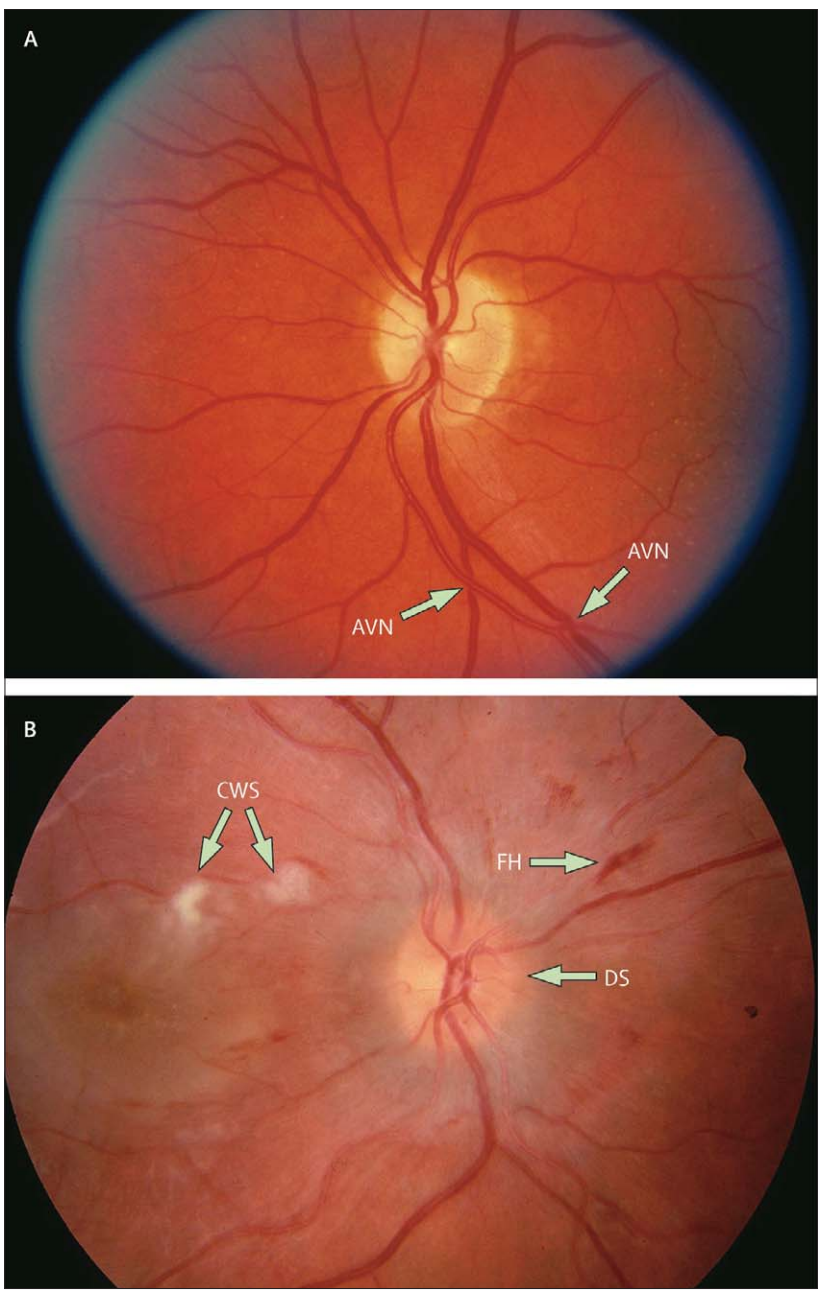


***Figure 1:*** **(A) Signs of mild hypertensive retinopathy in an eye with ischaemic optic neuropathy. (B) Signs of severe hypertensive retinopathy**
CWS=cotton-wool spots. FH=flame-shaped retina haemorrhage. DS=swelling of the optic disc. AVN=arteriovenous nipping.

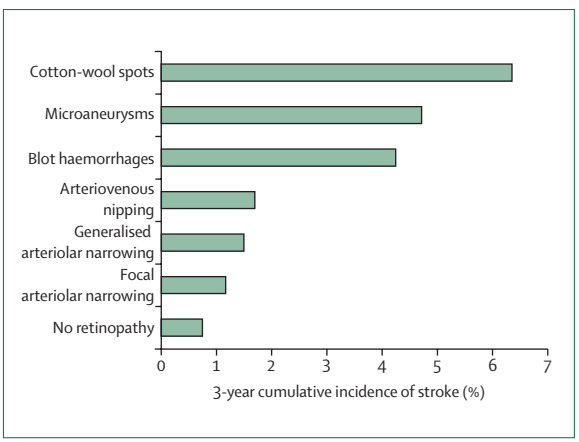


***Figure 2:*** **Relation between signs of hypertensive retinopathy and 3-year incident stroke**
Based on data from the Atherosclerosis Risk In Communities (ARIC) Study.[23]

Generalised retinal–arteriolar narrowing and arteriovenous nipping are related not only to a patient's current blood pressure levels, but also to levels measured in the past, suggesting that these signs are persistent markers of chronic hypertensive damage.[15,16,18] By contrast, focal arteriolar narrowing, retinal haemorrhages, microaneurysms, and cotton-wool spots have been associated only with concurrently measured blood pressure, and so might represent transient blood pressure changes.[16] Retinal–arteriolar narrowing might also be used to predict subsequent development of hypertension in individuals initially classified as normotensive.[19–21] Thus, retinal–arteriolar narrowing, possibly indicating more widespread peripheral vasoconstriction, could be an early marker of overt hypertension.

Hypertensive retinopathy has long been regarded as a marker of systemic vascular disease elsewhere in the body. The hypothesis of a link between hypertensive retinopathy and stroke has been the most consistent, and has been supported by anatomical, physiological, and pathological studies.[1,2,22] In a 3-year population-based cohort study of atherosclerosis risk, incident stroke events were more common in participants with signs of hypertensive retinopathy than in participants without retinopathy (figure 2).[23] In an analysis that controlled for blood pressure, diabetes, lipids, and other risk factors, moderate signs of hypertensive retinopathy (cotton-wool spots, retinal haemorrhages, and microaneurysms) were associated with a two-fold to four-fold higher risk of incident stroke.[23] Weaker associations between signs of mild hypertensive retinopathy and risk of stroke were also seen.[23] This study and others have now linked signs of hypertensive retinopathy with cognitive decline,[24] cerebral white-matter lesions identified by cerebral MRI,[25] lacunar infarctions,[26] cerebral atrophy,[27] and stroke mortality.[28,29]

Although studies of the association between hypertensive retinopathy signs and heart disease have produced inconsistent results,[30] various symptoms of hypertensive retinopathy have been linked with coronary-artery stenosis on angiography,[31] and with incident coronary heart-disease events in both men[32] and women.[33] Some investigators suggest that moderate hypertensive retinopathy could be used to predict incident congestive heart failure, even in individuals without a previous history of myocardial infarction.[34] Retinopathy signs have also been associated with other indicators of hypertensive target-organ damage, such as microalbuminuria and renal impairment[35,36] and left ventricular hypertrophy.[37]

Various national guidelines for management of hypertension recommend assessment of retinopathy to enable risk stratification.[38,39] Patients with mild retinopathy will probably only need routine care, whereas patients with moderate signs might benefit from further assessment of blood-pressure control (eg, home or 24-hour blood-pressure monitoring), assessment of other vascular risk (eg, cholesterol levels) and, if clinically indicated, appropriate risk-reduction therapy (eg, cholesterol-lowering agents). In patients with borderline or so-called white coat hypertension, physicians could interpret mild or moderate signs of retinopathy as evidence for end-organ damage, and as an indication that antihypertensive therapy could aid in treatment. Additionally, in patients with established hypertension, signs of retinopathy could suggest a need for close observation of blood pressure, supplementary anti-hypertensive therapy, or both. Patients with severe retinopathy need urgent antihypertensive management.

Evidence suggests treatment of hypertension could reverse the changes seen with retinopathy. Laboratory studies in animals[40] and clinical case series[41] have shown regression of retinopathy signs with control of blood pressure. However, whether regression of hypertensive retinopathy is accompanied by a reduction in cardio-vascular risk remains uncertain. We also need to know whether specific medications, such as those thought to improve microvascular structure and function (eg, angiotension-converting enzyme [ACE] inhibitors and statins), would reduce retinopathy damage beyond the effects of lowered blood pressure and lowered cholesterol alone. If so, use of such medications in patients with hypertensive retinopathy could also have additional therapeutic value in prevention and treatment of cardiovascular diseases.

## Hypertension as a risk factor in ocular disease

### Retinal vein occlusion

Hypertension predisposes patients to development of retinal vein occlusion, a common, sight-threatening retinal–vascular disorder.[42–45] Retinal vein occlusion is characterised clinically by dilatated and tortuous retinal veins and the presence of retinal haemorrhages, cotton-wool spots, and oedema of the macula and optic disc. These features are seen either in all four quadrants (central retinal vein occlusion; figure 3A), or in only one (branch retinal vein occlusion; figure 3B). Central retinal vein occlusion occurs in both ischaemic and non-ischaemic forms. Patients with an ischaemic central retinal vein occlusion typically present with poor visual acuity and a relative afferent papillary defect. Fluoroscein angiography of the fundus can show capillary non-perfusion. These patients have a poorer visual prognosis and are at risk of secondary neovascular glaucoma.[46]

Epidemiological studies of retinal vein occlusion in the general population are rare.[43–45] Population-based surveys[43,44] generally indicate that central retinal vein occlusions arise in 0·1–0·4% and branch retinal vein occlusions in 0·6–1·1% of adults aged 40 years and older. The 10-year cumulative incidence was reported to be 0·4% for central retinal vein occlusions and 1·2% for branch retinal vein occlusions.[47]

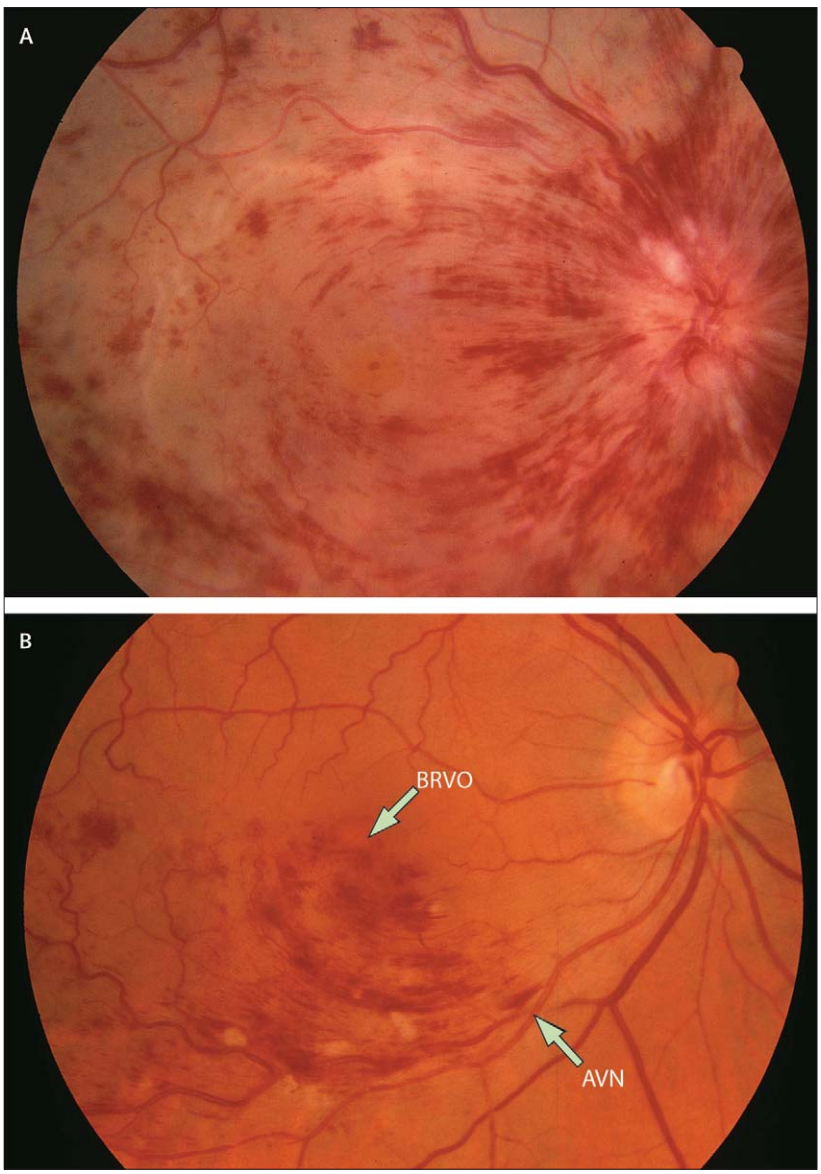


*Figure 3:* **(A) Central retinal vein occlusion. (B) Branch retinal vein occlusion**
AVN=arteriovenous nipping. BRVO=branch retinal vein occlusion.

Almost all relevant studies have recorded a strong and consistent link between hypertension and the risk of a retinal vein occlusion.[42–46] One investigation showed that participants with hypertension were five times more likely to have a branch retinal vein occlusion than those without hypertension.[43] Moreover, mild hypertensive retinopathy was strongly correlated with branch retinal vein occlusion, with an odds ratio of 17 for focal arteriolar narrowing, and 23 for arteriovenous nipping (figure 3B).[43] Retinal vein

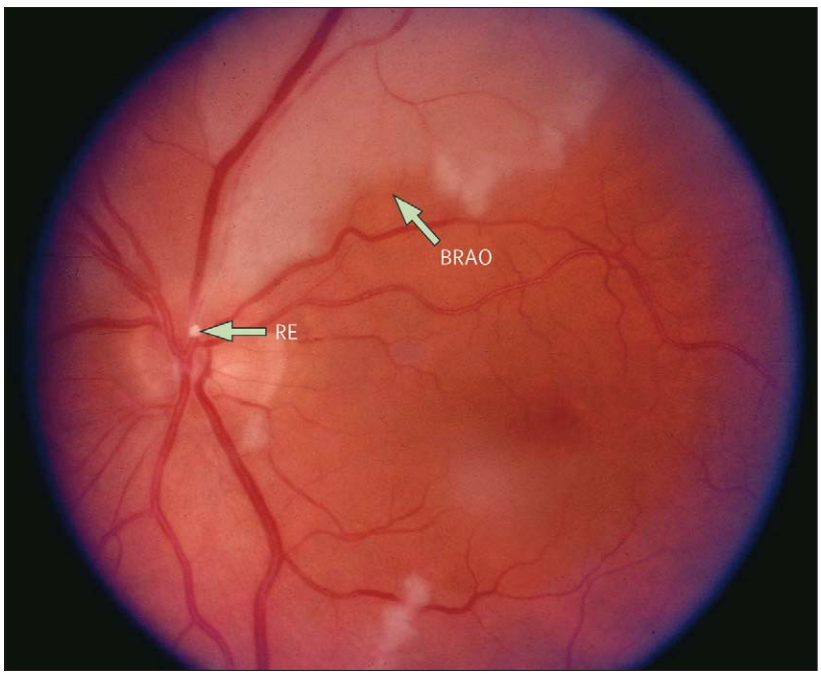


*Figure 4:* **Retinal–arteriolar emboli and retina branch artery occlusion**
RE=retinal emboli. BRAO=branch retinal artery occlusion.

occlusion is also associated with other cardiovascular risk factors, including diabetes,[42–44] cigarette smoking,[43–45] carotid artery disease,[45] and various haematological abnormalities (eg, hyperhomocysteinaemia, anticardiolipin antibodies, protein S and C deficiencies, activated protein C resistance, and factor V Leiden mutation).[48–50] Retinal vein occlusion has also been linked with stroke,[51] coronary heart disease,[44] and cardiovascular mortality.[52]

Management of patients with a retinal vein occlusion should include assessment of blood pressure control, standard cardiovascular risk factors, and haematological function. Ophthalmic follow-up is needed to diagnose and prevent the two main complications of retinal vein occlusion: neovascularisation and macular oedema. Randomised clinical trials have shown that prophylactic panretinal laser treatment does not necessarily prevent neovascularisation in ischaemic vein occlusions, and that laser treatment can be withheld unless the patient develops frank ocular neovascularisation.[53,54] Focal laser treatment can assist, however, in prevention of visual loss in some patients with macular oedema from branch retinal vein occlusion,[55] but does not seem to benefit macular oedema associated with central retinal vein occlusion.[56] Several treatment strategies for macular oedema (eg, injection of steroids or antivascular endothelial growth factor agents into the vitreous[57]) have been proposed, but their effectiveness and safety will need to be confirmed by randomised clinical trials. Although treatment of hypertension has not been proven to reduce the risk of complications associated with retinal vein occlusion, or prevent the development of this disorder in the unaffected eye, physicians should more closely monitor blood pressure and consider initiation or modification of therapy in patients with this eye disorder.

### Retinal emboli

Retinal–arteriolar emboli are discrete plaque-like lesions, lodged in the lumen of retinal arterioles.[58] These emboli are heterogeneous, and can be composed of cholesterol crystals (reflective emboli) or fibrin, platelets, calcium, or other materials (non-reflective emboli).[59] Retinal emboli can be single or multiple, and can be seen in one or both eyes.[60]

Epidemiological studies report that asymptomatic retinal emboli are fairly common in adults aged 40 years and older. Two large population-based studies have reported prevalence rates of 1·3% and 1·4%,[61,62] and the 10-year incidence of retinal emboli has been recorded as 2·9%.[63] Asymptomatic retinal emboli are often transient; in one study 90% of retinal emboli detected in baseline photographs were not present 5 years later.[64] The main risk factors for retinal emboli are hypertension, diabetes, and cigarette smoking.[46,61–65] In Australia, investigators showed that individuals with hypertension had a two-fold higher risk of prevalent and incident retinal emboli than those without hypertension,[61,63] but that this risk was increased to six-fold higher in hypertensive people who also smoked cigarettes.[66]

Retinal emboli have two important clinical implications. First, the distal portions of occluded arterioles could be ischaemic, and thus, could result in frank retinal artery occlusion (figure 4). Second, people with retinal emboli have a higher risk of thromboembolic stroke and cardiovascular disease.[62,64,66,67] In one study, participants with retinal emboli were twice as likely to have prevalent coronary heart disease and four times as likely to have carotid artery plaque as those without emboli.[45] Another study associated the presence of retinal emboli with a two-fold higher risk of stroke mortality, independent of blood pressure and other risk factors.[64]

Because of their increased risk of cardiovascular disease, patients with retinal emboli will need thorough systemic assessment, concentrating on hypertension control and other modifiable vascular risk factors. Although the source of the emboli (eg, carotid or cardiac) should be identified, the value of carotid ultrasonography or transthoracic echocardiography for detection of this source in asymptomatic patients remains controversial. Some studies suggest that up to 80% of people with asymptomatic retinal emboli do not have substantial carotid stenosis.[65] The usefulness of carotid endarterectomy in asymptomatic retinal emboli in patients with major carotid artery stenosis is also uncertain.[65] Patients with retinal emboli and atrial fibrillation will need systemic anticoagulation treatment.

### Retinal artery occlusion

Retinal artery occlusion occurs commonly in patients with hypertension.[46,68,69] Central retinal artery occlusion

presents with a sudden, painless, unilateral loss of vision and typically appears as a cherry red spot (figure 5). Occlusion of a branch retinal artery, by contrast, could present with a visual-field defect, and loss of central vision can be slight (figure 4). In up to 70% of cases of branch retinal artery occlusion retinal emboli is visible in the vessels at the optic disc, or downstream in branch retinal arterioles; these signs are present in about 20% of cases when the occlusion arises centrally.[68,69]

On the basis of clinic outpatient data, the yearly incidence of central retinal artery occlusion has been estimated at about one in 10 000, occurring typically in people aged 60–65 years.[68] However, a population-based study showed a significantly lower incidence of only 0·07 per 10 000 people per year.[70] Retinal artery occlusion is associated with hypertension and other cardiovascular risk factors, with haematological abnormalities, and with both subclinical and clinical stroke.[46,68,71,72] Nearly half the patients with retinal artery occlusion in one study were reported to have echocardiographic abnormalities, and 10% needed systemic treatment.[73] The disorder has been associated with an increased risk of cardiovascular disease and mortality.[71] In a prospective study of 99 patients with retinal artery occlusions followed-up for a mean duration of 4·2 years, the absolute risk of death was estimated at 8% per year; coronary events caused 60% of the deaths, and stroke only 3%.[74] Mortality rates might also vary due to the presence of retinal emboli; a study of 86 patients with retinal artery occlusions showed that mortality rates for those without visible retinal emboli were similar to age–sex controls, whereas patients with visible emboli had substantially higher mortality than controls.[75]

Thorough cardiovascular and cerebrovascular assessments, including analysis of carotid and cardiac images, are necessary for patients who present with retinal artery occlusions. The presence of retinal emboli has low predictive power for detection of significant carotid-artery stenosis, and thus should not affect decisions to do carotid ultrasonography.[76] Central retinal artery occlusion is usually regarded as an ocular emergency. Attempts to restore ocular circulation and preserve vision include rapid dislodgement of the embolus by digital massage of the eyeball; paracentesis to remove anterior chamber fluid and lower intraocular pressure; and breathing into a paper bag to induce carbon-dioxide-related vasodilation.[77,78] More aggressive treatment strategies such as selective ophthalmic artery fibrinolysis via the femoral artery have been suggested, but their effectiveness has yet to be proved.[79–81]

## Retinal macroaneurysm

Retinal arterial macroaneurysm, a fusiform or sacular dilatation of the retinal arterioles, is an uncommon disorder almost always seen in patients with hypertension.[82–84] In one hypothesis for the cause of retinal macroaneurysm, the retinal–arterial walls become less elastic with ageing, as both the medial muscle fibres and intima are gradually replaced by collagen. This decrease in elasticity renders the arterioles susceptible to dilatation caused by raised blood pressure. Hypertensive patients, with impaired autoregulation, are at particular risk. Subsequently, loss of the muscular coat, with thinning and fibrosis of arterial walls could lead to dilatation, hyperpermeability, and finally rupture of the macroaneurysm.

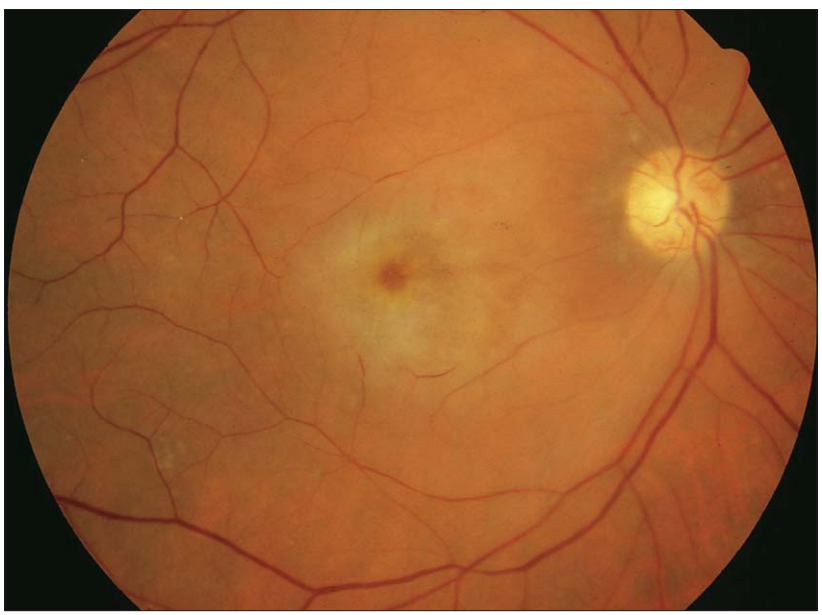

*Figure 5:* **Central retinal artery occlusion**

Data from large case series suggest that about a fifth of macroaneurysms are bilateral, and one in ten are multiple.[82] Macroaneurysm is usually an incidental finding in asymptomatic patients, but can also present acutely, with visual loss secondary to haemorrhage or exudation. Hypertension has been reported in up to 75% of patients with macroaneurysms.[82] Patients with uncontrolled hypertension might initially present with visual loss caused by macroaneurysm.[84] Visual recovery typically occurs spontaneously with thrombosis of the macroaneurysm and resolution of the haemorrhage and exudate.[84] However, residual retinal damage from chronic macular oedema and hard exudate deposition might lead to persistent poor vision. Anecdotal data suggest that laser treatment could be useful in some cases, especially when exudation affects the macula.

## Ischaemic optic neuropathy

Like the retinal circulation, optic nerve circulation is prone to the effects of hypertension and other vascular risk factors.[85] Ischaemic optic neuropathy is the most frequent acute optic neuropathy in patients aged over 50 years.[86] Either the anterior or the posterior segment of optic nerve can be affected. Anterior ischaemic optic neuropathy accounts for 90% of cases, and typically presents with sudden visual loss and optic-disc oedema

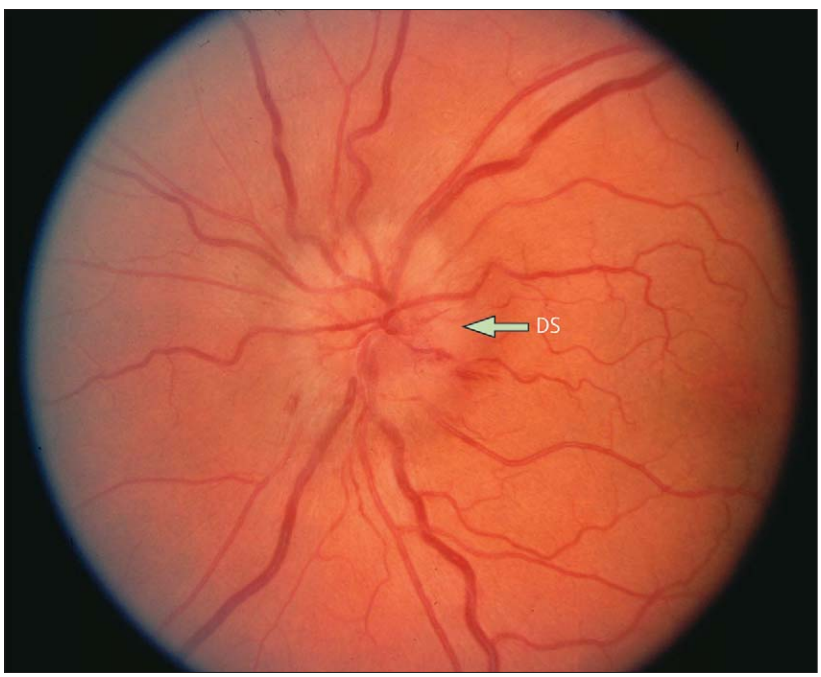


*Figure 6:* **Ischaemic optic neuropathy**
DS=disc swelling.

(figure 6), which is typically absent in posterior ischaemic optic neuropathy. Anterior ischaemic optic neuropathy can be further subdivided into arteritic and non-arteritic types, of which the arteritic form is typically due to giant-cell temporal arteritis, which is not associated with hypertension. By contrast, non-arteritic anterior ischaemic optic neuropathy has been strongly linked with hypertension and other cardiovascular risk factors.[87–89] One US study showed that the yearly incidence of non-arteritic anterior ischaemic optic neuropathy was 10·3 per 100 000 people aged 50 years and older.[90]

Clinical series show that up to 50% of patients with non-arteritic anterior ischaemic optic neuropathy might have hypertension and 25% might have diabetes.[91] Furthermore, hypertension, diabetes, and hypercholesterolaemia seem to increase the risk of anterior ischaemic optic neuropathy in younger patients more than they do in older patients.[87,89] By comparison with retinal artery occlusions, anterior ischaemic optic neuropathies are less usually associated with ipsilateral large-vessel carotid artery disease, and thus carotid ultrasound is not routinely needed.

Non-arteritic anterior ischaemic optic neuropathy has no known effective treatment. Optic-nerve sheath decompression surgery was thought to improve vision in some patients, but this treatment was not supported by the findings of a trial,[92] which showed that surgery did not improve visual outcome and was potentially harmful. Visual recovery after non-arteritic anterior ischaemic optic neuropathy is often limited, but spontaneous improvement of vision did occur in patients during the first year of this trial.[92]

## Diabetic retinopathy

Diabetic retinopathy is the most specific microvascular complication of diabetes and one of the main causes of visual impairment, especially in people of working-age.[93] A population-based study in the USA[94] suggested that 33% of diabetic people aged 40 years and older have retinopathy, and 8% have vision-threatening retinopathy. Diabetic retinopathy has an early, non-proliferative stage and a more advanced proliferative stage. Raised blood pressure is an independent risk factor for both the initial development of retinopathy and its subsequent progression. Impaired retinal–vascular autoregulation in response to high blood pressure plays a part in this association, since diabetic patients with hypertension seem to be less able to regulate retinal blood flow than non-diabetic patients.[95] In diabetes, hypertension can also result in endothelial damage in the retinal vasculature[96] and increased expression of vascular–endothelial growth factors.[97]

Epidemiological studies in individuals with diabetes provided initial evidence that hypertension might be important in development and progression of retinopathy. However, a relation between high blood pressure and retinopathy was seen in some,[98–101] but not all[102,103] studies. In a population-based study, high blood pressure was associated with an increased 14-year rate of diabetic retinopathy in participants with type 1 diabetes,[102] independent of baseline retinopathy status, glycosylated haemoglobin, duration of diabetes, and other risk factors. However, in participants with type 2 diabetes, neither systolic nor diastolic blood pressure was related to the incidence and progression of retinopathy.[104] Other studies recorded associations between the severity of diabetic retinopathy severity and systolic (but not diastolic) blood pressure,[104,105] and showed that such associations tended to weaken with increased age.[106] The variability of these results could indicate differences in study design, effects of selection bias in clinic-based studies, selective mortality in older patients with type 2 diabetes, or measurement errors in the assessment and definition of hypertension.

Clinical trial data subsequently provided clear and consistent evidence of the role of hypertension in the development and progression of diabetic retinopathy. In a prospective study in the UK,[107] 1048 patients with hypertension were randomly assigned to a regimen of tight control (aiming for blood-pressure levels below 150/85 mm Hg with atenolol or captopril) or less tight control (blood pressure below 180/105 mm Hg). Investigators noted that participants under tight blood-pressure control, had reductions of 37% in risk of microvascular disease, 34% in rate of progression of retinopathy, and 47% in deterioration of visual acuity.[107] Atenolol and captopril proved equally effective for decreasing the risk of microvascular complications,[107] which suggests that reduction of blood pressure per se was more important than the type of medication used. Importantly, the effects of blood pressure control were independent of glycaemia.[107] After 6 years of follow-up, participants in

this study with baseline blood pressure in the highest third of the population (systolic blood pressures >140 mm Hg) were three times as likely to develop retinopathy as those in the lowest third (systolic blood pressures <125 mm Hg).[108] No threshold systolic blood pressure was identified for this association,[108] but the data suggested that for each 10 mm Hg reduction in systolic blood pressure, the risk of retinopathy might fall by 10%.[107] Longer term follow-up of patients in this study have lent support to the early results.[109]

In general, data from epidemiological studies and clinical trials lend support to clinical recommendations that control of hypertension and blood pressure in patients with type 2 diabetes should help to prevent retinopathy and other microvascular complications. A randomised controlled clinical trial showed that intensive blood pressure control was more beneficial than conventional control for normotensive patients with type 2 diabetes but not for hypertensive patients.[110] Another study showed that in patients with type 2 diabetes and microalbuminuria, an intensive, multifactorial approach that targeted hyperglycaemia, hypertension, and dyslipidaemia, reduced the risk of retinopathy by 60%, compared with conventional treatment alone.[111]

Reduction of blood pressure, even in the normotensive range, could potentially lessen the risk of diabetic retinopathy. The results of one study showed that in patients with type 1 diabetes who were normotensive, and who had no evidence of microalbuminuria, treatment with an ACE inhibitor, reduced the progression of retinopathy by 50% over a 2-year period, after adjustment for glycaemic control.[112] Progression to proliferative retinopathy was also reduced by 80% in the group given ACE inhibitor compared with controls. However, these results have been criticised because the placebo group had significantly higher levels of mean glycosylated haemoglobin than the treatment group, even though this difference was adjusted in statistical analyses. This study suggested that ACE inhibitors might have an additional beneficial effect in prevention of retinopathy—independent of reduction of blood pressure. This additional benefit was postulated to be mediated via a more favourable retinal–haemodynamic profile, enhancement of nitric oxide production, reduction of endothelial dysfunction, blockage of vascular endothelial growth factors, and reduction of activity by matrix metalloproteinases.

## Ocular diseases where hypertension is a potential risk factor

### Age-related macular degeneration

Age-related macular degeneration is the most common cause of visual impairment in patients aged 65 years and older in developed countries.[93] Visual loss from age-related macular degeneration typically results from either neovascularisation associated with choroidal vessels (commonly termed wet or exudative age-related macular degeneration) or geographic atrophy of the retina.

Some have suggested that hypertension could increase the potential risk factor for age-related macular degeneration, on the basis of its purported effects on the choroidal circulation.[113,114] An association between hypertension and risk of age-related macular degeneration has been noted in both cross-sectional[115,116] and prospective data,[117,118] but has not been shown consistently in all studies.[119] One study, the Beaver Dam Eye Study,[119] reported that raised systolic blood pressure at baseline was not related to prevalent age-related macular degeneration, but did increase the 10-year risk of the disorder.[117] Another study, the Blue Mountains study in Australia,[120] has shown that focal arteriolar narrowing, a marker of hypertensive retinopathy damage, was associated with the incidence of some signs of age-related macular degeneration. Many of the risk factors for cardiovascular disease (such as cigarette smoking,[121–123] carotid artery disease,[118] and systemic markers of inflammation[124]) also predispose patients to this disorder. Furthermore, the disorder has been linked with a high risk of stroke[125] and cardiovascular mortality.[126]

A wide range of treatment options for age-related macular degeneration, including vascular endothelial growth-factor inhibitors, have been developed in the past decade.[127] However, specific antihypertensive medication or treatments to lower blood pressure have not proven beneficial for prevention of the development or progression of disorder. Observational studies suggest that antihypertensive medications do not affect the risk of this disorder.[128]

### Glaucoma

Glaucoma is a group of disorders characterised by progressive damage to the optic nerve and loss of visual field. This disorder is the second leading cause of irreversible blindness worldwide, and affects more than 50 million people.[93] The main risk factor for glaucoma is high intraocular pressure. Systemic hypertension is suspected to increase the risk of the development and progression of glaucoma. Several pathophysiological mechanisms have been proposed to explain this putative association.[129] First, direct microvascular damage from systemic hypertension could impair blood flow to the anterior optic nerve.[130,131] This notion is supported by studies linking glaucoma to abnormal ocular blood flow[132,133] and narrowing of the retinal vasculature.[134,135] Second, hypertension could interfere with autoregulation of the posterior ciliary circulation, which is already impaired in glaucoma.[136] Third, antihypertensive treatment could induce hypotensive episodes, especially at night,[137,138] which could reduce blood flow to the optic-nerve head, resulting in additional damage to the optic nerve. Fourth, other cardiovascular risk factors linked with hypertension (eg, diabetes[139,140] and cardiovascular disease[141]) could affect vascular perfusion of the optic-nerve head. Finally, systemic blood pressure is closely related to intraocular pressure,[142–145] the main risk factor for glaucomatous optic-nerve damage.

Epidemiological studies have not, however, shown a consistent association between hypertension and glaucoma.[146–151] Three population-based studies reported a cross-sectional association.[146–148] In one, people with hypertension were 50% more likely to have glaucoma, after adjustment for glaucoma risk factors such as intraocular pressure, than those without.[148] Hypertension also accounted for the greatest population-attributable risk for glaucoma compared with other risk factors,[148] suggesting that from a public-health perspective, hypertension might be more important than less common risk factors carrying a two-fold to three-fold higher risk of glaucoma. Nonetheless, prospective studies have not proven an association between either systolic or diastolic blood pressure and incidence of glaucoma.[150,151]

Part of the difficulty in understanding the link between blood pressure and glaucoma is the distinction between the independent effects of blood pressure with intraocular pressure, and the difference between the two (perfusion pressure). One study noted that low perfusion pressure (low systemic blood pressure combined with high intraocular pressure) was a stronger risk factor for glaucoma than was systemic hypertension per se.[152] Further, hypertension was a risk factor for glaucoma in older participants, but not in those who were younger.[152] This finding could indicate that the damaging effects of hypertension vary with age—ie, in younger people, raised blood pressure could protect against glaucoma, since in this age group, retinal vessels have not yet undergone chronic microvascular damage.

In terms of clinical management, physicians should be aware of the association between blood pressure and intraocular pressure. Whether treatment with antihypertensive medications can prevent progression of glaucoma is unclear. Improved blood pressure control in individuals susceptible to intraocular pressure could possibly help to stabilise glaucoma.

## Future directions and conclusions

Hypertension affects a large proportion of the adult population worldwide, and has widespread effects on the eye. We argue that any patient with hypertension should have an ophthalmological assessment to detect hypertensive retinopathy or other retinal vascular complications. Individuals with moderate hypertensive retinopathy (eg, flame-shaped or blot-shaped haemorrhages, cotton wool spots, hard exudates, microaneurysms, or a combination of these) are at increased risk of cardiovascular disease, independently of standard risk factors. Nonetheless, several questions remain. First, no standardised hypertensive retinopathy classification system has been accepted for use in primary-care settings, has good reproducibility, and can show validity in predicting cardiovascular events. Furthermore, although studies have suggested that retinal photography might be more precise than clinical ophthalmoscopy for the detection of signs of mild retinopathy, no study has compared different methods of retinal assessment. In the absence of new data, physicians are encouraged to continue the practice of fundoscopy for hypertensive patients when indicated, and referral for an ophthalmological consultation when findings are equivocal. No evidence exists to back up a recommendation that all hypertensive patients should be routinely referred for an eye consultation. Second, in view of the substantial racial and ethnic variation in the prevalence and effect of hypertension, we need to understand the ocular effects of blood pressure in different racial and ethnic groups. Finally, we will need to find out if intensive blood-pressure control in patients with hypertensive eye diseases could reduce the risk of visual and systemic morbidity. Blood pressure control has been established as a treatment for diabetic retinopathy, but requires evaluation for other eye disorders linked with hypertension. Recognition of the ocular effects of hypertension could assist physicians in the overall management of hypertension and damage to target end-organs.

**Contributors**

T Y Wong did the literature review, and drafted the manuscript. P Mitchell made critical revisions to the manuscript, and provided additional figures. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit the paper for publication.

**Conflict of interest statement**

We declare that we have no conflict of interest.

**Acknowledgments**

T Y Wong has received funding from NIH grant R21-HL077166, the National Heart Foundation, and the Sylvia and Charles Viertel Clinical Investigator Award, Australia. These funding sources had no role in the study design; in the collection, analysis, or interpretation of data; or in the writing of the report.

**References**

1 Wong TY, Klein R, Klein BE, Tielsch JM, Hubbard L, Nieto FJ. Retinal microvascular abnormalities and their relationship with hypertension, cardiovascular disease, and mortality. *Surv Ophthalmol* 2001; **46:** 59–80.

2 Tso MO, Jampol LM. Pathophysiology of hypertensive retinopathy. *Ophthalmol* 1982; **89:** 1132–45.

3 Klein R, Sharrett AR, Klein BE, et al. Are retinal arteriolar abnormalities related to atherosclerosis?: The Atherosclerosis Risk in Communities Study. *Arterioscler Thromb Vasc Biol* 2000; **20:** 1644–50.

4 Delles C, Michelson G, Harazny J, Oehmer S, Hilgers KF, Schmieder RE. Impaired endothelial function of the retinal vasculature in hypertensive patients. *Stroke* 2004; **35:** 1289–93.

5 Tsai WC, Li YH, Huang YY, Lin CC, Chao TH, Chen JH. Plasma vascular endothelial growth factor as a marker for early vascular damage in hypertension. *Clinl Sci* 2005; **109:** 39–43.

6 Keith NM, Wagener HP, Barker NW. Some different types of essential hypertension: their course and prognosis. *Am J Med Sci* 1974; **268:** 336–45.

7 Dimmitt SB, West JN, Eames SM, Gibson JM, Gosling P, Littler WA. Usefulness of ophthalmoscopy in mild to moderate hypertension. *Lancet* 1989; **1:** 1103–06.

8 Wong TY, Mitchell P. Hypertensive retinopathy. *N Engl J Med* 2004; **351:** 2310–17.

9 Klein R, Klein BE, Moss SE, Wang Q. Hypertension and retinopathy, arteriolar narrowing, and arteriovenous nicking in a population. *Arch Ophthalmol* 1994; **112:** 92–98.

10 Yu T, Mitchell P, Berry G, Li W, Wang JJ. Retinopathy in older persons without diabetes and its relationship to hypertension. *Arch Ophthalmol* 1998; **116:** 83–89.

11 Wong TY, Klein R, Klein BE, Meuer SM, Hubbard LD. Retinal vessel diameters and their associations with age and blood pressure. *Invest Ophthalmol Vis Sci* 2003; **44:** 4644–50.

12 Wang JJ, Mitchell P, Leung H, Rochtchina E, Wong TY, Klein R. Hypertensive retinal vessel wall signs in a general older population: the Blue Mountains Eye Study. *Hypertension* 2003; **42:** 534–41.

13 Klein R, Klein BE, Moss SE. The relation of systemic hypertension to changes in the retinal vasculature: the Beaver Dam Eye Study. *Trans Am Ophthalmol Soc* 1997; **95:** 329–48.

14 Hubbard LD, Brothers RJ, King WN, et al. Methods for evaluation of retinal microvascular abnormalities associated with hypertension/sclerosis in the Atherosclerosis Risk in Communities Study. *Ophthalmol* 1999; **106:** 2269–80.

15 Sharrett AR, Hubbard LD, Cooper LS, et al. Retinal arteriolar diameters and elevated blood pressure: the Atherosclerosis Risk in Communities Study. *Am J Epidemiol* 1999; **150:** 263–70.

16 Wong TY, Hubbard LD, Klein R, et al. Retinal microvascular abnormalities and blood pressure in older people: the Cardiovascular Health Study. *Br J Ophthalmol* 2002; **86:** 1007–13.

17 Wong TY, Knudtson MD, Klein R, Klein BE, Meuer SM, Hubbard LD. Computer-assisted measurement of retinal vessel diameters in the Beaver Dam Eye Study: methodology, correlation between eyes, and effect of refractive errors. *Ophthalmol* 2004; **111:** 1183–90.

18 Leung H, Wang JJ, Rochtchina E, Wong TY, Klein R, Mitchell P. Impact of current and past blood pressure on retinal arteriolar diameter in an older population. *J Hypertens* 2004; **22:** 1543–49.

19 Wong TY, Klein R, Sharrett AR, et al. Retinal arteriolar diameter and risk for hypertension. *Ann Intern Med* 2004; **140:** 248–55.

20 Wong TY, Shankar A, Klein R, Klein BE, Hubbard LD. Prospective cohort study of retinal vessel diameters and risk of hypertension. *BMJ* 2004; **329:** 79.

21 Smith W, Wang JJ, Wong TY, et al. Retinal arteriolar narrowing is associated with 5-year incident severe hypertension: the Blue Mountains Eye Study. *Hypertens* 2004; **44:** 442–47.

22 Patton N, Aslam T, Macgillivray T, Pattie A, Deary IJ, Dhillon B. Retinal vascular image analysis as a potential screening tool for cerebrovascular disease: a rationale based on homology between cerebral and retinal microvasculatures. *J Anat* 2005; **206:** 319–48.

23 Wong TY, Klein R, Couper DJ, et al. Retinal microvascular abnormalities and incident stroke: the Atherosclerosis Risk in Communities Study. *Lancet* 2001; **358:** 1134–40.

24 Wong TY, Klein R, Sharrett AR, et al. Retinal microvascular abnormalities and cognitive impairment in middle-aged persons: the Atherosclerosis Risk in Communities Study. *Stroke* 2002; **33:** 1487–92.

25 Wong TY, Klein R, Sharrett AR, et al. Cerebral white matter lesions, retinopathy, and incident clinical stroke. *JAMA* 2002; **288:** 67–74.

26 Kwa VI, van der Sande JJ, Stam J, Tijmes N, Vrooland JL, Amsterdam Vascular Medicine G. Retinal arterial changes correlate with cerebral small-vessel disease. *Neurology* 2002; **59:** 1536–40.

27 Wong TY, Mosley TH Jr, Klein R, et al. Retinal microvascular changes and MRI signs of cerebral atrophy in healthy, middle-aged people. *Neurology* 2003; **61:** 806–11.

28 Wong TY, Klein R, Nieto FJ, et al. Retinal microvascular abnormalities and 10-year cardiovascular mortality: a population-based case-control study. *Ophthalmol* 2003; **110:** 933–40.

29 Mitchell P, Wang JJ, Wong TY, Smith W, Klein R, Leeder SR. Retinal microvascular signs and risk of stroke and stroke mortality. *Neurology* 2005; **65:** 1005–09.

30 van den Born BJ, Hulsman CA, Hoekstra JB, Schlingemann RO, van Montfrans GA. Value of routine funduscopy in patients with hypertension: systematic review. *BMJ* 2005; **331:** 73.

31 Michelson EL, Morganroth J, Nichols CW, MacVaugh H 3rd. Retinal arteriolar changes as an indicator of coronary artery disease. *Arch Intern Med* 1979; **139:** 1139–41.

32 Duncan BB, Wong TY, Tyroler HA, Davis CE, Fuchs FD. Hypertensive retinopathy and incident coronary heart disease in high risk men. *Br J Ophthalmol* 2002; **86:** 1002–06.

33 Wong TY, Klein R, Sharrett AR, et al. Retinal arteriolar narrowing and risk of coronary heart disease in men and women. The Atherosclerosis Risk in Communities Study. *JAMA* 2002; **287:** 1153–59.

34 Wong TY, Rosamond W, Chang PP, et al. Retinopathy and risk of congestive heart failure. *JAMA* 2005; **293:** 63–69.

35 Wong TY, Coresh J, Klein R, et al. Retinal microvascular abnormalities and renal dysfunction: the atherosclerosis risk in communities study. *J Am Soc Neph* 2004; **15:** 2469–76.

36 Cuspidi C, Meani S, Salerno M, et al. Retinal microvascular changes and target organ damage in untreated essential hypertensives. *J Hypertens* 2004; **22:** 2095–102.

37 Saitoh M, Matsuo K, Nomoto S, et al. Relationship between left ventricular hypertrophy and renal and retinal damage in untreated patients with essential hypertension. *Int Med* 1998; **37:** 576–80.

38 Williams B, Poulter NR, Brown MJ, et al. British Hypertension Society guidelines for hypertension management 2004 (BHS-IV): summary. *BMJ* 2004; **328:** 634–40.

39 Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA* 2003; **289:** 2560–72.

40 Morishita R, Higaki J, Nakamura F, et al. Regression of hypertension-induced vascular hypertrophy by an ACE inhibitor and calcium antagonist in the spontaneously hypertensive rat. *Blood Pressure* 1992; **3** (suppl): 41–47.

41 Bock KD. Regression of retinal vascular changes by antihypertensive therapy. *Hypertens* 1984; **6:** 158–62.

42 Hayreh SS, Zimmerman B, McCarthy MJ, Podhajsky P. Systemic diseases associated with various types of retinal vein occlusion. *Am J Ophthalmol* 2001; **131:** 61–77.

43 Klein R, Klein BE, Moss SE, Meuer SM. The epidemiology of retinal vein occlusion: the Beaver Dam Eye Study. *Trans Am Ophthalmol Soc* 2000; **98:** 133–41.

44 Mitchell P, Smith W, Chang A. Prevalence and associations of retinal vein occlusion in Australia. The Blue Mountains Eye Study. *Arch Ophthalmol* 1996; **114:** 1243–47.

45 Wong TY, Larsen EK, Klein R, et al. Cardiovascular risk factors for retinal vein occlusion and arteriolar emboli: the Atherosclerosis Risk in Communities and Cardiovascular Health studies. *Ophthalmol* 2005; **112:** 540–47.

46 Hayreh SS. Prevalent misconceptions about acute retinal vascular occlusive disorders. *Prog Retin Eye Res* 2005; **24:** 493–519.

47 Cugati S, Wang JJ, Rochtchina E, Mitchell P. Ten year incidence of retinal vein occlusion in an older population: The Blue Mountains Eye Study. *Arch Ophthalmol* 2006; **124:** 726–32.

48 Greiner K, Hafner G, Dick B, Peetz D, Prellwitz W, Pfeiffer N. Retinal vascular occlusion and deficiencies in the protein C pathway. *Am J Ophthalmol* 1999; **128:** 69–74.

49 Gottlieb JL, Blice JP, Mestichelli B, Konkle BA, Benson WE. Activated protein C resistance, factor V Leiden, and central retinal vein occlusion in young adults. *Arch Ophthalmol* 1998; **116:** 577–79.

50 Chua B, Kifley A, Wong TY, Mitchell P. Homocysteine and retinal vein occlusion: a population-based study. *Am J Ophthalmol* 2005; **139:** 181–82.

51 Ueda Y, Kanazawa S, Ohira A, et al. Retinal vascular obstruction and asymptomatic cerebral infarction. *Jpn J Ophthalmol* 2002; **46:** 209–14.

52 Tsaloumas MD, Kirwan J, Vinall H, et al. Nine year follow-up study of morbidity and mortality in retinal vein occlusion. *Eye* 2000; **14:** 821–27.

53 The Central Vein Occlusion Study Group: N report. A randomized clinical trial of early panretinal photocoagulation for ischemic central vein occlusion. *Ophthalmol* 1995; **102:** 1434–44.

54 The Branch Vein Occlusion Study Group. Argon laser scatter photocoagulation for prevention of neovascularization and vitreous hemorrhage in branch vein occlusion. A randomized clinical trial. *Arch Ophthalmol* 1986; **104:** 34–41.

55 The Branch Vein Occlusion Study Group. Argon laser photocoagulation for macular edema in branch vein occlusion. *Am J Ophthalmol* 1984; **98:** 271–82.

56 The Central Vein Occlusion Study Group. M report. Evaluation of grid pattern photocoagulation for macular edema in central vein occlusion. *Ophthalmol* 1995; **102:** 1425–33.

57 Jonas JB, Kreissig I, Degenring R. Intravitreal triamcinolone acetonide for treatment of intraocular proliferative, exudative, and neovascular diseases. *Prog Retin Eye Res* 2005; **24:** 587–611.

58 Hollenhorst R. Significance of bright plaques in the retinal arterioles. *JAMA* 1961; **178:** 23–29.

59 de Bono DP, Warlow CP. Potential sources of emboli in patients with presumed transient cerebral or retinal ischaemia. *Lancet* 1981; **1:** 343–46.

60 Wong TY, Klein R. Retinal arteriolar emboli: epidemiology and risk of stroke. *Curr Opin Ophthalmol* 2002; **13:** 142–46.

61 Mitchell P, Wang JJ, Li W, Leeder SR, Smith W. Prevalence of asymptomatic retinal emboli in an Australian urban community. *Stroke* 1997; **28:** 63–66.

62 Klein R, Klein BE, Jensen SC, Moss SE, Meuer SM. Retinal emboli and stroke: the Beaver Dam Eye Study. *Arch Ophthalmol* 1999; **117:** 1063–68.

63 Cugati S, Wang JJ, Rochtchina E, Mitchell P. Ten-Year incidence of retinal emboli in an older population. *Stroke* 2006; **37:** 908–10.

64 Klein R, Klein BE, Moss SE, Meuer SM. Retinal emboli and cardiovascular disease: the Beaver Dam Eye Study. *Arch Ophthalmol* 2003; **121:** 1446–51.

65 Bruno A, Russell PW, Jones WL, Austin JK, Weinstein ES, Steel SR. Concomitants of asymptomatic retinal cholesterol emboli. *Stroke* 1992; **23:** 900–02.

66 Mitchell P, Wang JJ, Smith W. Risk factors and significance of finding asymptomatic retinal emboli. *Clin Exper Ophthalmol* 2000; **28:** 13–17.

67 Bruno A, Jones WL, Austin JK, Carter S, Qualls C. Vascular outcome in men with asymptomatic retinal cholesterol emboli. A cohort study. *Ann Intern Med* 1995; **122:** 249–53.

68 Recchia FM, Brown GC. Systemic disorders associated with retinal vascular occlusion. *Curr Opin Ophthalmol* 2000; **11:** 462–67.

69 Wilson LA, Warlow CP, Russell RW. Cardiovascular disease in patients with retinal arterial occlusion. *Lancet* 1979; **1:** 292–94.

70 Ivanisevic M, Karelovic D. The incidence of central retinal artery occlusion in the district of Split, Croatia. *Ophthalmologica* 2001; **215:** 245–46.

71 Patz A. Current concepts in ophthalmology. Retinal vascular diseases. *N Engl J Med* 1978; **298:** 1451–54.

72 Wijman CA, Gomes JA, Winter MR, et al. Symptomatic and asymptomatic retinal embolism have different mechanisms. *Stroke* 2004; **35:** e100–02.

73 Sharma S, Naqvi A, Sharma SM, Cruess AF, Brown GC. Transthoracic echocardiographic findings in patients with acute retinal arterial obstruction. A retrospective review. Retinal Emboli of Cardiac Origin Group. *Arch Ophthalmol* 1996; **114:** 1189–92.

74 Hankey GJ, Slattery JM, Warlow CP. Prognosis and prognostic factors of retinal infarction: a prospective cohort study. *BMJ* 1991; **302:** 499–504.

75 Savino PJ, Glaser JS, Cassady J. Retinal stroke. Is the patient at risk? *Arch Ophthalmol* 1977; **95:** 1185–89.

76 Sharma S, Brown GC, Pater JL, Cruess AF. Does a visible retinal embolus increase the likelihood of hemodynamically significant carotid artery stenosis in patients with acute retinal arterial occlusion? *Arch Ophthalmol* 1998; **116:** 1602–06.

77 Atebara NH, Brown GC, Cater J. Efficacy of anterior chamber paracentesis and Carbogen in treating acute nonarteritic central retinal artery occlusion. *Ophthalmol* 1995; **102:** 2029–34.

78 Rumelt S, Dorenboim Y, Rehany U. Aggressive systematic treatment for central retinal artery occlusion. *Am J Ophthalmol* 1999; **128:** 733–38.

79 Weber J, Remonda L, Mattle HP, et al. Selective intra-arterial fibrinolysis of acute central retinal artery occlusion. *Stroke* 1998; **29:** 2076–79.

80 Mueller AJ, Neubauer AS, Schaller U, Kampik A, European Assessment Group for Lysis in the E. Evaluation of minimally invasive therapies and rationale for a prospective randomized trial to evaluate selective intra-arterial lysis for clinically complete central retinal artery occlusion. *Arch Ophthalmol* 2003; **121:** 1377–81.

81 Arnold M, Koerner U, Remonda L, et al. Comparison of intra-arterial thrombolysis with conventional treatment in patients with acute central retinal artery occlusion. *J Neurol Neurosurg Psychiatry* 2005; **76:** 196–99.

82 Rabb MF, Gagliano DA, Teske MP. Retinal arterial macroaneurysms. *Surv Ophthalmol* 1988; **33:** 73–96.

83 Panton RW, Goldberg MF, Farber MD. Retinal arterial macroaneurysms: risk factors and natural history. *Br J Ophthalmol* 1990; **74:** 595–600.

84 Brown DM, Sobol WM, Folk JC, Weingeist TA. Retinal arteriolar macroaneurysms: long-term visual outcome. *Br J Ophthalmol* 1994; **78:** 534–38.

85 Hayreh SS. Blood flow in the optic nerve head and factors that may influence it. *Prog Retin Eye Res* 2001; **20:** 595–624.

86 Rucker JC, Biousse V, Newman NJ. Ischemic optic neuropathies. *Curr Opin Neurol* 2004; **17:** 27–35.

87 Hayreh SS, Joos KM, Podhajsky PA, Long CR. Systemic diseases associated with nonarteritic anterior ischemic optic neuropathy. *Am J Ophthalmol* 1994; **118:** 766–80.

88 Guyer DR, Miller NR, Auer CL, Fine SL. The risk of cerebrovascular and cardiovascular disease in patients with anterior ischemic optic neuropathy. *Arch Ophthalmol* 1985; **103:** 1136–42.

89 Jacobson DM, Vierkant RA, Belongia EA. Nonarteritic anterior ischemic optic neuropathy. A case-control study of potential risk factors. *Arch Ophthalmol* 1997; **115:** 1403–07.

90 Hattenhauer MG, Leavitt JA, Hodge DO, Grill R, Gray DT. Incidence of nonarteritic anterior ischemic optic neuropathy. *Am J Ophthalmol* 1997; **123** (1): 103–7.

91 The Ischemic Optic Neuropathy Decompression Trial Research Group. Characteristics of patients with nonarteritic anterior ischemic optic neuropathy eligible for the Ischemic Optic Neuropathy Decompression Trial. *Arch Ophthalmol* 1996; **114:** 1366–74.

92 The Ischemic Optic Neuropathy Decompression Trial Research Group. Optic nerve decompression surgery for nonarteritic anterior ischemic optic neuropathy (NAION) is not effective and may be harmful. *JAMA* 1995; **273:** 625–32.

93 Congdon N, Friedman DS, Lietman T. Important causes of visual impairment in the world today. *JAMA* 2003; **290:** 2057–60.

94 Wong TY, Klein R, Islam FM, et al. Diabetic retinopathy in a multi-ethnic cohort in the United States. *Am J Ophthalmol* 2006; **141:** 446–55.

95 Rassam SM, Patel V, Kohner EM. The effect of experimental hypertension on retinal vascular autoregulation in humans: a mechanism for the progression of diabetic retinopathy. *Exp Physiol* 1995; **80:** 53–68.

96 Hsueh WA, Anderson PW. Hypertension, the endothelial cell, and the vascular complications of diabetes mellitus. *Hypertens* 1992; **20:** 253–63.

97 Suzuma I, Hata Y, Clermont A, et al. Cyclic stretch and hypertension induce retinal expression of vascular endothelial growth factor and vascular endothelial growth factor receptor-2: potential mechanisms for exacerbation of diabetic retinopathy by hypertension. *Diabetes* 2001; **50:** 444–54.

98 Klein R, Klein BE, Moss SE, Davis MD, DeMets DL. The Wisconsin epidemiologic study of diabetic retinopathy. II. Prevalence and risk of diabetic retinopathy when age at diagnosis is less than 30 years. *Arch Ophthalmol* 1984; **102:** 520–26.

99 Klein R, Klein BE, Moss SE, Davis MD, DeMets DL. The Wisconsin epidemiologic study of diabetic retinopathy. III. Prevalence and risk of diabetic retinopathy when age at diagnosis is 30 or more years. *Arch Ophthalmol* 1984; **102:** 527–32.

100 Klein R, Klein BE, Moss SE, Davis MD, DeMets DL. The Wisconsin epidemiologic study of diabetic retinopathy. IV. Diabetic macular edema. *Ophthalmol* 1984; **91:** 1464–74.

101 Kostraba JN, Klein R, Dorman JS, et al. The epidemiology of diabetes complications study. IV. Correlates of diabetic background and proliferative retinopathy. *Am J Epidemiol* 1991; **133:** 381–91.

102 Klein R, Klein BE, Moss SE, Cruickshanks KJ. The Wisconsin Epidemiologic Study of Diabetic Retinopathy: XVII. The 14-year incidence and progression of diabetic retinopathy and associated risk factors in type 1 diabetes. *Ophthalmol* 1998; **105:** 1801–15.

103 Klein R, Sharrett AR, Klein BE, et al. The association of atherosclerosis, vascular risk factors, and retinopathy in adults with diabetes : the atherosclerosis risk in communities study. *Ophthalmol* 2002; **109:** 1225–34.

104 Klein R, Klein BE, Moss SE, Davis MD, DeMets DL. Is blood pressure a predictor of the incidence or progression of diabetic retinopathy? *Arch Intern Med* 1989; **149:** 2427–32.

105 Harris MI, Klein R, Cowie CC, Rowland M, Byrd-Holt DD. Is the risk of diabetic retinopathy greater in non-Hispanic blacks and Mexican Americans than in non-Hispanic whites with type 2 diabetes? A U.S. population study. *Diabetes Care* 1998; **21:** 1230–35.

106 Klein R, Marino EK, Kuller LH, et al. The relation of atherosclerotic cardiovascular disease to retinopathy in people with diabetes in the Cardiovascular Health Study. *Br J Ophthalmol* 2002; **86:** 84–90.

107 UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. *BMJ* 1998; **317:** 703–13.

108 Adler AI, Stratton IM, Neil HA, et al. Association of systolic blood pressure with macrovascular and microvascular complications of type 2 diabetes (UKPDS 36): prospective observational study. *BMJ* 2000; **321:** 412–19.

109 Matthews DR, Stratton IM, Aldington SJ, Holman RR, Kohner EM, Group UKPDS. Risks of progression of retinopathy and vision loss related to tight blood pressure control in type 2 diabetes mellitus: UKPDS 69. *Arch Ophthalmol* 2004; **122:** 1631–40.

110 Estacio RO, Jeffers BW, Gifford N, Schrier RW. Effect of blood pressure control on diabetic microvascular complications in patients with hypertension and type 2 diabetes. *Diabetes Care* 2000; **23** (suppl 2)**:** 54–64.

111 Gaede P, Vedel P, Parving HH, Pedersen O. Intensified multifactorial intervention in patients with type 2 diabetes mellitus and microalbuminuria: the Steno type 2 randomised study. *Lancet* 1999; **353:** 617–22.

112 The EUCLID Study Group. Randomised placebo-controlled trial of lisinopril in normotensive patients with insulin-dependent diabetes and normoalbuminuria or microalbuminuria. *Lancet* 1997; **349:** 1787–92.

113 Age-Related Eye Disease Study Research G. Risk factors associated with age-related macular degeneration. A case-control study in the age-related eye disease study: Age-Related Eye Disease Study Report Number 3. *Ophthalmol* 2000; **107:** 2224–32.

114 Miyazaki M, Nakamura H, Kubo M, et al. Risk factors for age related maculopathy in a Japanese population: the Hisayama study. *Br J Ophthalmol* 2003; **87:** 469–72.

115 Hyman L, Schachat AP, He Q, Leske MC. Hypertension, cardiovascular disease, and age-related macular degeneration. Age-Related Macular Degeneration Risk Factors Study Group. *Arch Ophthalmol* 2000; **118:** 351–58.

116 The Eye Disease Case-Control Study Group. Risk factors for neovascular age-related macular degeneration. *Arch Ophthalmol* 1992; **110:** 1701–08.

117 Klein R, Klein BE, Tomany SC, Cruickshanks KJ. The association of cardiovascular disease with the long-term incidence of age-related maculopathy: the Beaver Dam Eye Study. *Ophthalmol* 2003; **110:** 1273–80.

118 van Leeuwen R, Ikram MK, Vingerling JR, Witteman JC, Hofman A, de Jong PT. Blood pressure, atherosclerosis, and the incidence of age-related maculopathy: the Rotterdam Study. *Invest Ophthalmol Vis Sci* 2003; **44:** 3771–77.

119 Klein R, Klein BE, Franke T. The relationship of cardiovascular disease and its risk factors to age-related maculopathy. The Beaver Dam Eye Study. *Ophthalmol* 1993; **100:** 406–14.

120 Wang JJ, Mitchell P, Rochtchina E, Tan AG, Wong TY, Klein R. Retinal vessel wall signs and the 5 year incidence of age related maculopathy: the Blue Mountains Eye Study. *Br J Ophthalmol* 2004; **88:** 104–09.

121 Snow KK, Seddon JM. Do age-related macular degeneration and cardiovascular disease share common antecedents? *Ophthalmic Epidemiol* 1999; **6:** 125–43.

122 Klein R, Klein BE, Jensen SC. The relation of cardiovascular disease and its risk factors to the 5-year incidence of age-related maculopathy: the Beaver Dam Eye Study. *Ophthalmol* 1997; **104:** 1804–12.

123 Smith W, Mitchell P, Leeder SR. Smoking and age-related maculopathy. The Blue Mountains Eye Study. *Arch Ophthalmol* 1996; **114:** 1518–23.

124 Seddon JM, Gensler G, Milton RC, Klein ML, Rifai N. Association between C-reactive protein and age-related macular degeneration. *JAMA* 2004; **291:** 704–10.

125 Wong TY, Klein R, Sun C, et al. Age-related macular degeneration and risk of stroke. *Ann Int Med* 2006; **145:** 98–106.

126 Clemons TE, Kurinij N, Sperduto RD, Group AR. Associations of mortality with ocular disorders and an intervention of high-dose antioxidants and zinc in the Age-Related Eye Disease Study: AREDS Report No. 13. *Arch Ophthalmol* 2004; **122:** 716–26.

127 Gragoudas ES, Adamis AP, Cunningham ET Jr, Feinsod M, Guyer DR, Group VISiONCT. Pegaptanib for neovascular age-related macular degeneration. *N Engl J Med* 2004; **351:** 2805–16.

128 van Leeuwen R, Tomany SC, Wang JJ, et al. Is medication use associated with the incidence of early age-related maculopathy? Pooled findings from 3 continents. *Ophthalmol* 2004; **111:** 1169–75.

129 Langman M, Lancashire R, Cheng K, Stewart PM. Systemic hypertension and glaucoma: mechanisms in common and co-occurrence. *Br J Ophthalmol* 2005; **89:** 960–3.

130 Flammer J, Orgul S, Costa VP, et al. The impact of ocular blood flow in glaucoma. *Prog Retin Eye Res* 2002; **21:** 359–93.

131 Piltz-seymour JR, Grunwald JE, Hariprasad SM, Dupont J. Optic nerve blood flow is diminished in eyes of primary open-angle glaucoma suspects. *Am J Ophthalmol* 2001; **132:** 63–69.

132 Fuchsjager-Mayrl G, Wally B, Georgopoulos M, et al. Ocular blood flow and systemic blood pressure in patients with primary open-angle glaucoma and ocular hypertension. *Invest Ophthalmol Vis Sci* 2004; **45:** 834–39.

133 Logan JF, Rankin SJ, Jackson AJ. Retinal blood flow measurements and neuroretinal rim damage in glaucoma. *Br J Ophthalmol* 2004; **88:** 1049–54.

134 Jonas JB, Nguyen XN, Naumann GO. Parapapillary retinal vessel diameter in normal and glaucoma eyes. I. Morphometric data. *Invest Ophthalmol Vis Sci* 1989; **30:** 1599–603.

135 Mitchell P, Leung H, Wang JJ, et al. Retinal vessel diameter and open-angle glaucoma: the Blue Mountains Eye Study. *Ophthalmol* 2005; **112:** 245–50.

136 Grunwald JE, Riva CE, Stone RA, Keates EU, Petrig BL. Retinal autoregulation in open-angle glaucoma. *Ophthalmol* 1984; **91:** 1690–94.

137 Graham SL, Drance SM, Wijsman K, Douglas GR, Mikelberg FS. Ambulatory blood pressure monitoring in glaucoma. The nocturnal dip. *Ophthalmol* 1995; **102:** 61–69.

138 Hayreh SS, Zimmerman MB, Podhajsky P, Alward WL. Nocturnal arterial hypotension and its role in optic nerve head and ocular ischemic disorders. *Am J Ophthalmol* 1994; **117:** 603–24.

139 Mitchell P, Smith W, Chey T, Healey PR. Open-angle glaucoma and diabetes: the Blue Mountains eye study, Australia. *Ophthalmol* 1997; **104:** 712–18.

140 Nakamura M, Kanamori A, Negi A. Diabetes mellitus as a risk factor for glaucomatous optic neuropathy. *Ophthalmologica* 2005; **219:** 1–10.

141 Hayreh SS. The role of age and cardiovascular disease in glaucomatous optic neuropathy. *Surv Ophthalmol* 1999; **43** (suppl 1)**:** 27–42.

142 Hennis A, Wu SY, Nemesure B, Leske MC, Barbados Eye Studies G. Hypertension, diabetes, and longitudinal changes in intraocular pressure. *Ophthalmol* 2003; **110:** 908–14.

143 Klein BE, Klein R, Knudtson MD. Intraocular pressure and systemic blood pressure: longitudinal perspective: the Beaver Dam Eye Study. *Br J Ophthalmol* 2005; **89:** 284–87.

144 Foster PJ, Machin D, Wong TY, et al. Determinants of intraocular pressure and its association with glaucomatous optic neuropathy in Chinese Singaporeans: the Tanjong Pagar Study. *Invest Ophthalmol Vis Sci* 2003; **44:** 3885–91.

145 Mitchell P, Lee AJ, Wang JJ, Rochtchina E. Intraocular pressure over the clinical range of blood pressure: Blue Mountains eye study findings. *Am J Ophthalmol* 2005; **140:** 131–32.

146 Dielemans I, Vingerling JR, Algra D, Hofman A, Grobbee DE, de Jong PT. Primary open-angle glaucoma, intraocular pressure, and systemic blood pressure in the general elderly population. The Rotterdam Study.[see comment]. *Ophthalmol* 1995; **102:** 54–60.

147 Bonomi L, Marchini G, Marraffa M, Bernardi P, Morbio R, Varotto A. Vascular risk factors for primary open angle glaucoma: the Egna-Neumarkt Study. *Ophthalmol* 2000; **107:** 1287–93.

148 Mitchell P, Lee AJ, Rochtchina E, Wang JJ. Open-angle glaucoma and systemic hypertension: the Blue Mountains eye study. *J Glaucoma* 2004; **13:** 319–26.

149 Wu SY, Leske MC. Associations with intraocular pressure in the Barbados Eye Study. *Arch Ophthalmol* 1997; **115:** 1572–76.

150 Leske MC, Wu SY, Nemesure B, Hennis A. Incident open-angle glaucoma and blood pressure. *Arch Ophthalmol* 2002; **120:** 954–59.

151 Le A, Mukesh BN, McCarty CA, Taylor HR. Risk factors associated with the incidence of open-angle glaucoma: the visual impairment project. *Invest Ophthalmol Vis Sci* 2003; **44:** 3783–89.

152 Tielsch JM, Katz J, Sommer A, Quigley HA, Javitt JC. Hypertension, perfusion pressure, and primary open-angle glaucoma. A population-based assessment. *Arch Ophthalmol* 1995; **113:** 216–21.