3rd Victor Yong Lecture

Retinal and Cardiovascular Diseases: The "Common Soil" Theory

Tien Y Wong,[1,2] *PhD, FRCSE, FRANZCO*

Abstract

Retinal and cardiovascular diseases share many risk factors, such as hypertension, hyperlipidaemia and cigarette smoking. The effects of hypertension and diabetes on the retina are well known. In response to elevated blood pressure, the retinal vasculature undergoes a series of changes clinically seen as hypertensive retinopathy. Patients with hypertensive retinopathy signs are more likely to develop stroke, ischaemic heart disease, heart failure and to die from these conditions. In persons with diabetes, retinopathy is a common microvascular complication and the leading cause of blindness in working adults. Hyperglycaemia, hypertension and hyperlipidaemia are risk factors for the development and progression of diabetic retinopathy, and the presence of even early signs of retinopathy is associated with increased cardiovascular morbidity in persons with diabetes. Various cardiovascular diseases have also been associated with the development of other retinal conditions, including retinal vein occlusions, retinal arteriolar emboli and age-related macular degeneration. Ophthalmologists and physicians should therefore recognise the protean effects of cardiovascular diseases on the retina to better manage their patients.

Ann Acad Med Singapore 2007;36(Suppl):4-8

Key words: Cardiovascular disease, Hypertension, Retina, Retinopathy

Introduction

There is increasing evidence that retinal and cardiovascular diseases share a "common soil". Risk factors for cardiovascular disease, such as hypertension, diabetes, hyperlipidaemia and cigarette smoking, are known to influence the development of a range of retinal diseases, including hypertensive retinopathy, diabetic retinopathy, retinal vein and artery occlusion, retinal arteriolar emboli and age-related macular degeneration (AMD). Concurrently, many of these retinal conditions may be "markers" of underlying subclinical vascular disease and predict the future development of cardiovascular events and mortality. Understanding the inter-relationship between retinal and the cardiovascular diseases will allow both researchers and clinicians to design new preventative strategies and therapies, and to better manage patients with these conditions. This review summarises recent findings on the relationship of cardiovascular disease and common retinal conditions.

Hypertensive Retinopathy

The retinal circulation undergoes a series of pathophysiological changes in response to elevated blood pressure, resulting in a spectrum of clinical signs commonly referred to as hypertensive retinopathy.[1] Hypertensive retinopathy can be classified into 3 grades of increasing severity,[2] consisting of "mild" retinopathy (retinal arteriolar signs such as generalised retinal arteriolar narrowing, focal arteriolar narrowing, arterio-venous nicking and arteriolar wall opacification or silver wiring), "moderate" retinopathy (blot and dot retinal haemorrhages, cotton wool spots, hard exudates and microaneurysms) and "severe" or "malignant" retinopathy (mild or moderate signs with optic disc swelling).

Recent studies using retinal photography to document hypertensive retinopathy signs show that these signs are common (up to 14% of the general non-diabetic adult population) and are strongly associated with elevated blood pressure.[3-6] Studies have also used computer imaging techniques to measure generalised retinal arteriolar narrowing and have shown this sign predicts the subsequent development of hypertension in individuals initially classified as "normotensive",[7-9] and may thus be an early marker of pre-clinical hypertension.

[1] Centre for Eye Research Australia, University of Melbourne, Australia
[2] Singapore Eye Research Institute, Yong Loo Lin School of Medicine, National University of Singapore, Singapore
Address for Correspondence: Professor Tien Y Wong, Centre for Eye Research Australia, University of Melbourne, 32 Gisborne Street, East Melbourne 3002, Australia.
Email: twong@unimelb.edu.au

Hypertensive retinopathy signs are markers of increased cardiovascular risk. There has been consistent association of hypertensive retinopathy with stroke.[1,10] In one large population-based study of more than 10,000 participants, patients with hypertensive retinopathy signs were 3 times more likely to develop a clinical stroke over a 3-year period than those without retinopathy.[11] In that study, while controlling for age, sex, race, mean arterial blood pressure, diabetes, and other stroke risk factors, retinal microvascular signs were predictive of incident stroke, with adjusted relative risks of 2.58 [95% confidence interval (CI), 1.59-4.20] for any retinopathy, 3.11 (95% CI, 1.71-5.65) for microaneurysms, 3.08 (95% CI, 1.42-6.68) for cotton wool spots, 2.55 (95% CI, 1.27-5.14) for blot haemorrhages, 2.26 (95% CI, 1.00-5.12) for flame-shaped haemorrhages, and 1.60 (95% CI, 1.03-2.47) for arteriovenous nicking. Other studies have now linked hypertensive retinopathy signs with cognitive decline,[12] subclinical cerebral disease,[13] small artery lacunar infarctions,[14] magnetic resonance imaging (MRI) defined cerebral atrophy,[15] and stroke mortality.[16,17]

Hypertensive retinopathy has also been linked with coronary artery stenosis as seen on angiography,[18] and with risk of clinical coronary events in both men[19] and women.[20] In a prospective study, "moderate" hypertensive retinopathy signs predicted a 3-fold higher incidence of congestive heart failure, even in patients without a previous myocardial infarction (relative risk 2.98; 95% CI, 1.50-5.92).[21] These associations suggest that microvascular disease may be important in the development of heart failure in the absence of established coronary artery occlusion.

Various international clinical guidelines for the management of hypertension support the value of a retinal assessment for cardiovascular risk stratification.[22] Patients with "mild" retinopathy will only require routine care. However, patients with "moderate" retinopathy may benefit from a more careful assessment of blood pressure control, evaluation of other vascular risk factors (e.g., cholesterol levels) and, if indicated, appropriate cardiovascular risk reduction therapy (e.g., cholesterol lowering drugs). Physicians should also examine the retina in the group of patients with "borderline" or "white coat" hypertension, where the presence of hypertensive retinopathy may serve as evidence of target end organ damage, thus providing the basis for initiating anti-hypertensive treatment. Patients with "severe" or "malignant" retinopathy will need urgent cardiovascular assessment and anti-hypertensive management, including possibly intravenous therapy.

There is some evidence that treatment of hypertension could reverse retinopathy changes,[23] but it remains unclear if regression of hypertensive retinopathy signs is accompanied by a reduction in cardiovascular risk. It is also uncertain if specific medications, such as those suggested to have direct beneficial effects on microvascular structure and function (e.g., angiotension-converting enzyme inhibitors), would reduce retinopathy damage beyond the effects of lowered blood pressure alone. If so, it is possible that such medications in patients with hypertensive retinopathy may have added therapeutic value in preventing and treating cardiovascular diseases.

Diabetic Retinopathy

In patients with either type 1 or type 2 diabetes, retinopathy is the most specific microvascular complication, and one of the leading causes of visual impairment, particularly in middle-aged persons.[24] Diabetic retinopathy can be broadly classified into an early stage of non-proliferative retinopathy and a later, more advanced stage of proliferative retinopathy.

The 3 classic risk factors for diabetic retinopathy are hyperglycaemia, hypertension and hyperlipidaemia. These cardiovascular risk factors have been shown to be important for both the initial development of diabetic retinopathy, the subsequent progression to advanced retinopathy.

Landmark clinical trials such as the United Kingdom Prospective Diabetes Study (UKPDS) show that blood pressure control is effective in preventing visual loss from diabetic retinopathy. In the UKPDS, "tight" blood pressure control reduced the rate of progression of diabetic retinopathy by 35%, and deterioration of visual acuity by 50%, and each 10 mm Hg reduction in systolic blood pressure was associated with a 10% reduction in the risk of retinopathy.[25] Furthermore, there is good evidence that controlling for multiple cardiovascular risk factors has added benefits. The Steno-2 Study showed that in patients with type 2 diabetes, an intensive, multifactorial approach that targeted hyperglycaemia, hypertension and dyslipidaemia, reduced the risk of retinopathy by 60% compared with conventional treatment alone.[26]

Diabetic retinopathy has also long been known to signal an increased risk of cardiovascular morbidity in patients. Numerous studies have now shown that patients with retinopathy have higher risk of stroke, coronary artery disease and cardiovascular mortality than patients without retinopathy, irrespective of glycaemic and blood pressure levels.[27-33] In a prospective study on more than 1500 patients with type 2 diabetes, even the presence of mild retinopathy signs were associated with a 2-fold higher risk of stroke (relative risk 2.34; 95% CI, 1.13 to 4.86).[34] In another long-term follow-up study, the risk of stroke was 6-fold higher and stroke mortality 2-fold higher in diabetic patients with proliferative retinopathy than those without any retinopathy.[35] These data suggest that both ophthalmologists and physicians should be aware that patients with diabetic retinopathy may warrant a more careful

cardiovascular assessment and follow-up.

Retinal Vein Occlusion

Retinal vein occlusion (RVO) is a common, sight-threatening retinal vascular condition characterised clinically by dilated and tortuous retinal veins and the presence of retinal haemorrhages, cotton wool spots, and macular and optic disc oedema. RVO and cardiovascular diseases share many similar risk factors.[36-38] Studies have documented strong and consistent relationships between hypertension and the risk of RVO.[36-38] One study suggested that patients with hypertension were 5 times as likely to have RVO as those without hypertension.[36] RVO is also associated with other cardiovascular risk factors, including diabetes,[36,37] cigarette smoking,[36-38] and carotid artery disease,[38] and has been linked with stroke and cardiovascular mortality.[37]

Patients with RVO should be evaluated for cardiovascular disease and risk factors such as blood pressure. It has been suggested that in young people (e.g., <40 years), assessment of possible haematological abnormalities (e.g., hyperhomocysteinaemia, anti-cardiolipin antibodies, protein S and C deficiencies, activated protein C resistance, and Factor V Leiden mutation) may also be indicated. However, the usefulness of these investigations requires further study. Although there is no evidence that treatment of cardiovascular risk factors would reduce the risk of complications associated with RVO, or prevent the development of RVO in the unaffected eye, physicians should consider this retinal condition as an indication to more closely monitor cardiovascular risk and to initiate or modify therapy.

Retinal Arteriolar Emboli and Retinal Artery Occlusion

Retinal arteriolar emboli are discrete plaque-like lesions that may be single or multiple, and are composed of cholesterol crystals or fibrin, platelets, calcium and other materials in the lumen of retinal arterioles. Asymptomatic retinal emboli are fairly common in older persons[39,40] but are often transient. In one study, 90% of emboli detected initially were not present 5 years later at follow-up.[41] Retinal emboli and cardiovascular disease also share a "common soil" with similar vascular risk factors, including hypertension, diabetes and cigarette smoking.[39-43] A population-based study in Australia showed that individuals with hypertension had a 2-fold higher risk of a retinal emboli than those without hypertension,[39,43] and amongst hypertensive persons who were also cigarette smokers, the risk was increased to 6 fold.[44]

It has long been known that patients with retinal arteriolar emboli have a higher risk of developing thrombo-embolic stroke and other cardiovascular events.[40,41,44,45] In one study, patients with retinal emboli were twice as likely to have coronary artery disease and 4 times as likely to have carotid artery plaque as those without emboli.[38]

Retinal artery occlusion is an uncommon consequence of emboli when the distal portions of the arterioles are fully occluded. Retinal artery occlusion is associated with a similar spectrum of cardiovascular risk factors, and may be a risk marker for stroke and cardiovascular mortality.[46,47] In one 4-year prospective study of patients with retinal artery occlusion, the absolute risk of death was 8% per year.[48] In another study, patients with retinal artery occlusion with visible emboli had significantly higher mortality than age-gender population controls, although the risk of death was not higher among patients with retinal artery occlusion without visible emboli.[49] Thus, the presence of emboli is important for prognosis.

Physicians and ophthalmologists should conduct a systemic cardiovascular assessment in patients with retinal emboli and/or retinal artery occlusion. Identifying the source of the emboli (e.g., carotid or cardiac source) is important, although some have questioned the utility of carotid ultrasonography and the benefit of carotid endarterectomy in patients with asymptomatic retinal emboli and significant carotid artery stenosis.[42] However, patients who have retinal emboli and detected to have atrial fibrillation may need systemic anti-coagulation.

Age-Related Macular Degeneration

AMD is the most common cause of visual impairment in patients aged 65 years and older in the Western world. AMD is characterised by the presence of drusen and pigmentary abnormalities (early AMD) with subsequent visual loss from progression of early to late AMD, involving either the development of new vessels in the choroid (commonly termed "wet" or exudative AMD) or geographic atrophy of the retina.

AMD and cardiovascular disease have also been suggested to share a "common soil". There is now good evidence that hypertension is a risk factor for AMD, supported by both cross-sectional[50,51] and prospective data.[52,53] AMD also shares many other cardiovascular risk factors, notably cigarette smoking,[54-56] carotid artery disease,[53] and systemic markers of inflammation.[57] The association of cigarette smoking with AMD is strong and consistent. In the Blue Mountains Eye Study, cigarette smoking was significantly associated with late AMD [odds ratio (OR), 3.92], including neovascular AMD (OR, 3.20) and geographic atrophy (OR, 4.54), and early age-related maculopathy (OR, 1.75).[56] In the Rotterdam study, an increase in carotid artery wall thickness (OR, 1.15; 95% CI, 1.03-1.28, per standard deviation increase in thickness) increased the risk of AMD.[53] In the Age-Related Eye Disease Study (AREDS), a multicentre randomised trial of antioxidant vitamins and

minerals, serum C-reactive protein levels were significantly higher among participants with advanced AMD than among those with no AMD.[57] In models adjusting for age, sex, smoking and body mass index, the OR for AMD was 1.65, comparing the highest versus the lowest quartile of C-reactive protein levels.

There is now evidence that the presence of AMD may also signify a higher risk for the development of stroke,[58] coronary artery disease,[59] and cardiovascular mortality.[60] This relationship is important as there have been a range of new treatment options for AMD, including the use of vascular endothelial growth factor (VEGF) inhibitors. These anti-VEGF inhibitors, even when administered into the eye (intra-vitreous injection), have been suggested to increase systemic haemorrhage, and may also increase cardiovascular risk.[61,62]

There is no data that shows if lowering blood pressure or controlling other vascular risk factors has beneficial effects in preventing AMD development or progression. There is some suggestion that statin use may reduce the risk of AMD, but this remains an important aspect of future research.[63]

Conclusions

This review highlights the close relationship between retinal and cardiovascular diseases, supporting a theory that they share a "common soil". Cardiovascular risk factors such as hypertension and diabetes have widespread effects on the retina, and retinal diseases in turn appear to be a marker of various subclinical and clinical cardiovascular diseases, including stroke and heart disease. Thus, ophthalmologists should be aware that patients with these retinal conditions may be at increased risk of developing cardiovascular diseases. Concurrently, general physicians should be encouraged to examine the retina in patients with cardiovascular risk factors.

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. Wong TY, Mitchell P. Hypertensive retinopathy. N Engl J Med 2004;351:2310-7.
3. Klein R, Klein BE, Moss SE, Wang Q. Hypertension and retinopathy, arteriolar narrowing, and arteriovenous nicking in a population. Arch Ophthalmol 1994;112:92-8.
4. Yu T, Mitchell P, Berry G, Li W, Wang JJ. Retinopathy in older persons without diabetes and its relationship to hypertension. Arch Ophthalmol 1998;116:83-9.
5. Wong TY, Klein R, Sharrett AR, Manolio TA, Hubbard LD, Marino EK, et al. The prevalence and risk factors of retinal microvascular abnormalities in older persons: The Cardiovascular Health Study. Ophthalmology 2003;110:658-66.
6. 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.
7. Wong TY, Klein R, Sharrett AR, Duncan BB, Couper DJ, Klein BE, et al. Retinal arteriolar diameter and risk for hypertension. Ann Intern Med 2004;140:248-55.
8. Wong TY. Is retinal photography useful in the measurement of stroke risk? Lancet Neurol 2004;3:179-83.
9. Smith W, Wang JJ, Wong TY, Rochtchina E, Klein R, Leeder SR, et al. Retinal arteriolar narrowing is associated with 5-year incident severe hypertension: the Blue Mountains Eye Study. Hypertension 2004;44: 442-7.
10. 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.
11. Wong TY, Klein R, Couper DJ, Cooper LS, Shahar E, Hubbard LD, et al. Retinal microvascular abnormalities and incident stroke: the Atherosclerosis Risk in Communities Study. Lancet 2001;358:1134-40.
12. Wong TY, Klein R, Sharrett AR, Nieto FJ, Boland LL, Couper DJ, et al. Retinal microvascular abnormalities and cognitive impairment in middle-aged persons: the Atherosclerosis Risk in Communities Study. Stroke 2002;33:1487-92.
13. Wong TY, Klein R, Sharrett AR, Couper DJ, Klein BE, Liao DP, et al. Cerebral white matter lesions, retinopathy, and incident clinical stroke. JAMA 2002;288:67-74.
14. 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.
15. Wong TY, Mosley TH, Jr., Klein R, Klein BE, Sharrett AR, Couper DJ, et al. Retinal microvascular changes and MRI signs of cerebral atrophy in healthy, middle-aged people. Neurology 2003;61:806-11.
16. Wong TY, Klein R, Nieto FJ, Klein BE, Sharrett AR, Meuer SM, et al. Retinal microvascular abnormalities and 10-year cardiovascular mortality: a population-based case-control study. Ophthalmology 2003;110: 933-40.
17. Mitchell P, Wang JJ, Wong TY, Smith W, Klein R, Leeder SR. Retinal microvascular signs and risk of stroke and stroke mortality. Neurology 2005;65:1005-9.
18. 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.
19. 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.
20. Wong TY, Klein R, Sharrett AR, Duncan BB, Couper DJ, Tielsch JM, et al. Retinal arteriolar narrowing and risk of coronary heart disease in men and women. The Atherosclerosis Risk in Communities Study. JAMA 2002;287:1153-9.
21. Wong TY, Rosamond W, Chang PP, Couper DJ, Sharrett AR, Hubbard LD, et al. Retinopathy and risk of congestive heart failure. JAMA 2005;293:63-9.
22. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, 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.
23. Bock KD. Regression of retinal vascular changes by antihypertensive therapy. Hypertension 1984;6(6 Pt 2):158-62.
24. Wong TY, Klein R, Islam FM, Cotch MF, Folsom AR, Klein BE, et al. Diabetic retinopathy in a multi-ethnic cohort in the United States. Am J Ophthalmol 2006;141:446-55.
25. 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.
26. Gaede P, Vedel P, Parving HH, Pedersen O. Intensified multifactorial intervention in patients with type 2 diabetes mellitus and microalbumin-

uria: the Steno type 2 randomised study. Lancet 1999;353:617-22.
27. Petitti D, Bhatt, H. Retinopathy as a risk factor for nonembolic stroke in diabetic subjects. Stroke 1995;26:593-6.
28. Iino K, Yoshinari M, Kaku K, Yamamoto M, Sato Y, Kodama T, et al. Prospective study of asymmetric retinopathy as a predictor of brain infarction in diabetes mellitus. Diabetes Care 1993;16:1405-6.
29. Klein R, Klein BE, Moss SE. Epidemiology of proliferative diabetic retinopathy. Diabetes Care 1992;15:1875-91.
30. Miettinen H, Haffner SM, Lehto S, Ronnemaa T, Pyorala K, Laakso M. Retinopathy predicts coronary heart disease events in NIDDM patients. Diabetes Care 1996;19:1445-8.
31. Cheung N, Wang JJ, Klein R, Couper DJ, Sharrett AR, Wong TY. Diabetic retinopathy and the risk of coronary heart disease: the Atherosclerosis Risk in Communities Study. Diabetes Care 2007; 30:1742-6.
32. Targher G, Bertolini L, Tessari R, Zenari L, Arcaro G. Retinopathy predicts future cardiovascular events among type 2 diabetic patients: The Valpolicella Heart Diabetes Study. Diabetes Care 2006;29:1178.
33. Juutilainen A, Lehto S, Ronnemaa T, Pyorala K, Laakso M. Retinopathy predicts cardiovascular mortality in type 2 diabetic men and women. Diabetes Care 2007;30:292-9.
34. Cheung N, Rogers S, Couper DJ, Klein R, Sharrett AR, Wong TY. Is diabetic retinopathy an independent risk factor for ischemic stroke? Stroke 2007;38:398-401.
35. Klein R, Klein BE, Moss SE, Cruickshanks KJ. Association of ocular disease and mortality in a diabetic population. Arch Ophthalmol 1999;117:1487-95.
36. 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;discussion 141-3.
37. Mitchell P, Smith W, Chang A. Prevalence and associations of retinal vein occlusion in Australia. The Blue Mountains Eye Study. Arch Ophthalmol 1996;114:1243-7.
38. Wong TY, Larsen EK, Klein R, Mitchell P, Couper DJ, Klein BE, et al. Cardiovascular risk factors for retinal vein occlusion and arteriolar emboli: the Atherosclerosis Risk in Communities & Cardiovascular Health studies. Ophthalmology 2005;112:540-7.
39. Mitchell P, Wang JJ, Li W, Leeder SR, Smith W. Prevalence of asymptomatic retinal emboli in an Australian urban community. Stroke 1997;28:63-6.
40. Klein R, Klein BE, Jensen SC, Moss SE, Meuer SM. Retinal emboli and stroke: the Beaver Dam Eye Study. Arch Ophthalmol 1999;117:1063-8.
41. Klein R, Klein BE, Moss SE, Meuer SM. Retinal emboli and cardiovascular disease: the Beaver Dam Eye Study. Arch Ophthalmol 2003;121: 1446-51.
42. Bruno A, Russell PW, Jones WL, Austin JK, Weinstein ES, Steel SR. Concomitants of asymptomatic retinal cholesterol emboli. Stroke 1992; 23:900-2.
43. Cugati S, Wang JJ, Rochtchina E, Mitchell P. Ten-Year incidence of retinal emboli in an older population. Stroke 2006;37:908-10.
44. Mitchell P, Wang JJ, Smith W. Risk factors and significance of finding asymptomatic retinal emboli. Clin Exp Ophthalmol 2000;28:13-7.
45. 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.
46. Hayreh SS. Prevalent misconceptions about acute retinal vascular occlusive disorders. Prog Retin Eye Res 2005;24:493-519.
47. Patz A. Current concepts in ophthalmology. Retinal vascular diseases. N Engl J Med 1978;298:1451-4.
48. Hankey GJ, Slattery JM, Warlow CP. Prognosis and prognostic factors of retinal infarction: a prospective cohort study. BMJ 1991;302: 499-504.
49. Savino PJ, Glaser JS, Cassady J. Retinal stroke. Is the patient at risk? Arch Ophthalmol 1977;95:1185-9.
50. 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: 351-8.
51. The Eye Disease Case-Control Study Group. Risk factors for neovascular age-related macular degeneration. Arch Ophthalmol 1992;110:1701-8.
52. 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. Ophthalmology 2003;110: 636-43.
53. 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;44:3771-7.
54. Snow KK, Seddon JM. Do age-related macular degeneration and cardiovascular disease share common antecedents? Ophthalmic Epidemiol 1999;6:125-43.
55. 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. Ophthalmology 1997;104:1804-12.
56. Smith W, Mitchell P, Leeder SR. Smoking and age-related maculopathy. The Blue Mountains Eye Study. Arch Ophthalmol 1996;114:1518-23.
57. 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.
58. Wong TY, Klein R, Sun C, Mitchell P, Couper DJ, Lai H, et al; Atherosclerosis Risk in Communities Study. Age-related macular degeneration and risk for stroke. Ann Intern Med 2006;145:98-106. Summary for patients in: Ann Intern Med 2006;145:I37.
59. Wong TY, Tikellis G, Sun C, Klein R, Couper DJ, Sharrett AR. Age-related macular degeneration and risk of coronary heart disease: the Atherosclerosis Risk in Communities Study. Ophthalmology 2007; 114:86-91.
60. 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.
61. Wong TY, Liew G, Mitchell P. Clinical update: new treatments for age-related macular degeneration. Lancet 2007;370:204-6.
62. Gillies MC, Wong TY. Ranibizumab for neovascular age-related macular degeneration. N Engl J Med 2007;356:748-9.
63. Wong TY, Rogers SL. Statins and age-related macular degeneration: time for a randomized controlled trial? Am J Ophthalmol 2007;144: 117-9.