MEDICAL CARDIOVASCULAR TREATMENT TRIALS: RELEVANT TO MEDICAL OPHTHALMOLOGY IN 1997?

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Despite extensive research and the availability of modern treatment methods, retinovascular disease and diabetic retinopathy remain amongst the leading causes of blindness and severe visual impairment in the Western world. Although the medical conditions underlying these retinopathies have been clearly established, strong confirmed trial evidence of the value of medical treatment has only become available in the 1990s. This was particularly the case in older patients with retinovascular disease or diabetic retinopathy, in whom the treatment of underlying cardiovascular risk factors had little trial evidence of benefit. The aim of this review is to present the impressive results from the most recent medical treatment trials, with emphasis on the relevance to retinovascular disease and diabetic retinopathy.

Retinal vein occlusion, retinal artery occlusion and non-arteritic anterior ischaemic optic neuropathy are the most common forms of retinovascular disease, whereas leakage, capillary closure, shunting, hyperperfusion and neovascularisation are the common retinovascular changes seen in diabetic retinopathy.¹

Large studies have highlighted the increased prevalence, compared with matched controls, of hypertension and hyperlipidaemia in the aetiology of retinal vein and retinal artery occlusion^{2,3} (Table I). Of patients presenting with these disorders according to type of occlusion (branch or central), 50–60% will be hypertensive and 40–50% will have underlying hyperlipidaemia (fasting serum cholesterol >6.5 mmol/l or triglyceride >2.1 mmol/l), predominantly hypercholesterolaemia. The most striking association has been noted in West Indian subjects with retinal vein occlusion, of whom 83%

were hypertensive.³ The potential importance of the most recent cardiovascular treatment trials is demonstrated by the finding that patients with retinal arterial or venous occlusion have a significant excess mortality from cardiovascular disease (myocardial infarction and cerebrovascular disease) on longer-term follow-up.^{3–8} Current evidence also suggests that recurrence in the fellow eye in patients with a single retinal vein occlusion may occur in 10–15% of subjects,^{9,10} which introduced the concept that treatment of underlying cardiovascular risk factors could prevent recurrence with avoidance of disastrous visual outcome.^{10,11}

In contrast to retinal vein occlusion, recurrence of retinal artery occlusion is uncommon, but longer-term follow-up has demonstrated significant mortality from myocardial infarction in these patients.⁵ Perhaps the best potential benefit of treatment of underlying cardiovascular risk factors could be in those patients with one episode of non-arteritic anterior ischaemic optic neuropathy.^{2,12,13} Longer-term follow-up studies of this patient group has demonstrated significant mortality from coronary and cerebrovascular disease, but has also highlighted a high recurrence rate in 25–75% of subjects in the fellow eye, with disastrous visual outcome.¹³

Although the exact mechanism causing basement membrane thickening of the retinal-endothelial cells in diabetes is still unclear, our understanding of the relationship between the retinal microvascular changes and systemic factors has been highlighted – for example treatment of hypertension delaying onset and progression of diabetic nephropathy.¹⁴ The recent treatment trials could have considerable impact on clinical management of patients with diabetic retinopathy, with emphasis on preventing visual loss.

A crucial question to medical ophthalmology is the consideration of retinovascular disease as target organ damage in relation to underlying cardiovascular

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Table I. Prevalence rates of underlying cardiovascular risk factors in patients with retinovascular disease

Prevalence rates of	Retinal artery occlusion		Retinal vein occlusion		Non-arteritic ischaemic optic neuropathy (n = 435)
	Branch (n = 71)	Central (n = 56)	Branch (n = 305)	Central (n = 235)	
Hypertension	59%	66%	63%	49%	39%
Hyperlipidaemia	50%	45%	50%	43%	51%
Diabetes mellitus	7%	5%	12%	8%	22%
Smoking (current at time of diagnosis)	45%	54%	37%	37%	51%
Data drawn from references	2,5,6	2,5,6	2,3,8	2,3,8	2,12,13
Mean age of patients (years)	63	65	63	65	67

n, patient numbers studied.
Hypertension defined by WHO criteria, hyperlipidaemia by British Hyperlipidaemia Association criteria and diabetes mellitus by WHO criteria.

risk factors. This is supported by pathological studies which have demonstrated that degenerative and atherosclerotic disease are the major aetiologies in retinal vein and artery occlusion and ischaemic optic neuropathy.² Data in diabetic patients will be considered separately.

New randomized controlled trials (RCT) will therefore be reviewed to discuss these issues in relation to individual cardiovascular risk factors. These include:

- Hypertension
- Hyperlipidaemia
- Diabetes mellitus
- Atheromatous carotid disease
- Anti-platelet and anti-coagulant drugs
- Others, e.g. hormone replacement therapy and smoking

Each individual prospective randomised medical treatment trial is not mentioned in this article, but a summary of the treatment trials (and meta-analysis where available) is included.

HYPERTENSION

There is a strong relationship between the presence of hypertension and the occurrence of retinovascular disease. However, many patients with retinovascular disease are >65 years of age, an age group in whom the benefit of hypotensive treatment in the 1980s was unclear. Many impressive treatment trials with large numbers of subjects have been published showing clear benefit of treatment of essential hypertension when blood pressure levels persistently exceed 160 mmHg systolic and 95 mmHg diastolic.¹⁵ However, this trial evidence was in patients under the age of 65 years. Meta-analysis demonstrated a 40% reduction in stroke and 14% reduction in coronary heart disease rates (less than the predicted 25%) with long-term antihypertensive drug treatment of essential hypertension.¹⁵

Two recent trials, reported in 1993 (STOP and SHEP), demonstrated the value of treatment of hypertension in elderly populations with either isolated systolic hypertension or combined systolic

and diastolic hypertension.¹⁶⁻¹⁸ The oldest patient in these trials was aged 85 years. Over a 5 year period, using thiazides and beta-blockers, a significant reduction in mortality as well as in coronary and cerebrovascular events was clearly demonstrated. As a result, hypertension societies across the world are recommending antihypertensive drug therapy for those with diastolic blood pressures >100 mmHg, up to the age of 80 years.^{19,20} In addition, they recommend more aggressive treatment in the elderly (>60 years of age) if the systolic blood pressure is ≥160 mmHg or diastolic pressure ≥90 mmHg. These more aggressive levels apply when target organ damage is present. All societies emphasise the importance of repeated measurements on several visits before considering the initiation of therapy, unless the blood pressure is distinctly elevated. Trials have also highlighted three points: (a) the higher the initial pressure, the greater the potential benefit, (b) benefit from lowering blood pressure is greater in patients with target organ damage, (c) the better the control of blood pressure on treatment, the better the outcome. Target levels of blood pressure to be achieved with therapy have been suggested to be 140 mmHg systolic and 90 mmHg diastolic by most national guidelines.

Data with regard to the treatment of accelerated hypertension are clear-cut, showing a major advantage of treatment of hypertension, such that 60-80% of patients should have at least a 5 year survival. These dramatically improved survival figures from the 10% 1 year survival without treatment in the 1930s, have required the re-classification of hypertensive retinopathy into two grades (grade A, non-accelerated hypertension; grade B, accelerated hypertension).²¹ The poor survival figures of untreated accelerated hypertension makes its identification a medical emergency requiring hospital admission.

Routine measurement of blood pressure has advanced with the advent of non-invasive ambulatory blood pressure monitoring (ABPM), which removes many of the inaccuracies of clinic blood pressure measurement.²⁰ ABPM has also been shown to relate more closely to a range of target

organ damage in hypertensive individuals than clinic blood pressure measurement.²¹ These include left ventricular hypertrophy, microalbuminuria, lacunar cerebral infarctions and retinovascular hypertensive changes.^{22–24} Prospective studies currently in progress may reinforce the increasing role of ABPM measurement in the management of hypertension.²⁵ ABPM is proving a useful technique in the management of patients with retinovascular disease, with a recent report showing the possible role of nocturnal hypotension in the aetiology of ischaemic optic neuropathy and retinal vein occlusion.²⁶

These data are of considerable importance in view of the high prevalence of hypertension underlying retinovascular disease. Occurrence of a retinovascular occlusion in a patient may be regarded as evidence of target organ damage, and should therefore prompt aggressive treatment of hypertension. This approach has the potential to reduce cerebrovascular and cardiac disease end-points and has been shown to reduce recurrence of retinovascular disease in one large follow-up study.⁴

The class of anti-hypertensive drug that should be used is less clear. The large treatment trials have used the established agents of thiazide diuretics (particularly in the elderly and at low dose), beta-blockers and vasodilators. The newer agents, i.e. calcium antagonists and angiotensin converting enzyme (ACE) inhibitors, have not been tested in large hypertension treatment trials demonstrating reduction of total mortality, coronary heart disease and stroke end-points. However, there is a suggestion from experimental and clinical trials that there may be advantages in the use of ACE inhibitors in the treatment of hypertension in association with retinal disease, as there is evidence of reduction of leakage from the retinal circulation,²⁷ as well as the possibility of reduction of angiogenic growth factors by this class of anti-hypertensives.²⁸

The potential benefit of treatment of hypertension associated with diabetes mellitus has not been proven with regard to retinopathy (see later), but ACE inhibitors are becoming the agents of choice in this patient group. The new class of anti-hypertensive drug, the angiotensin II receptor antagonists, may have additional potential to affect angiogenesis.²⁹

HYPERLIPIDAEMIA

Recent evidence has suggested that hypercholesterolaemia and hypertriglyceridaemia are associated with retinovascular disease. In particular, hypercholesterolaemia (fasting cholesterol 6.5 mmol/l) relates to the branch form of retinal vein occlusion, and ischaemic optic neuropathy, and is the predominant form underlying both branch and central retinal artery occlusion. Hypertriglyceridaemia (fasting

serum triglyceride >2.1 mmol/l) underlies retinovascular disease, but the prevalence rates (6–13%) are less impressive.² Two reports have suggested that other retinal changes – cotton wool spots (retinal infarction), capillary closure and vascular leakage – may occur in the presence of combined hyperlipidaemia, but that these microvascular changes are not observed in patients with familial hypercholesterolaemia.³⁰ Diabetic exudative maculopathy has been reported in association with an increased prevalence of hypercholesterolaemia and combined hyperlipidaemia.³¹ Preliminary data of treatment of early diabetic exudative maculopathy with modern lipid-lowering drug therapy have shown a reduction of exudation over a 1 year period.³²

With regard to macrovascular disease, positive associations between coronary artery disease and LDL-cholesterol, and negative (i.e. protective) associations with HDL-cholesterol and its subfraction HDL₂, have been demonstrated in population studies. Although fasting serum triglyceride levels do show a positive correlation with ischaemic heart disease this is not an independent risk factor on multivariate analysis.³³

Since 1978, results of at least eight large trials of lipid-lowering therapy in the prevention, either primary or secondary, of coronary heart disease have been published. Significant decreases in coronary heart disease occurred in all the trials using treatment with resins or fibrates, but there was a decrease in total mortality in only two secondary prevention trials up to 1994.³² Three meta-analyses have been performed combining data from all the primary and secondary trials comprising 125 000 patients.^{34–36} Overall, coronary heart disease was reduced by a factor of 2.5 compared with controls (a 1% reduction in cholesterol is associated with a 1.5% reduction in coronary heart disease events). The major issues confounding these results were the poor reduction in overall mortality and the increases in traumatic deaths and cancer rates (neither of which were statistically significant) and lack of data in women.^{35,36} The issue of total mortality is much argued, but in reality no single trial had been large enough to test this effect, and meta-analysis has not provided a clear answer.

In 1994 the 4S (the Scandinavian Simvastatin Survival Study) was published.³⁷ This 5 year secondary prevention trial in patients with hypercholesterolaemia treated with simvastatin versus placebo has shown impressive results. The simvastatin-treated group demonstrated a reduction in total mortality by 30%, coronary death by 42%, and all major coronary events by 34% when compared with the placebo group. Furthermore, there was no increase in traumatic or cancer deaths. These important data demonstrated the value of lipid-lowering drug

therapy (HMG-coA reductase inhibitors) in secondary prevention of macrovascular disease. The target cholesterol level in this study was 5.2 mmol/l, which was much lower than the previous target of 6.5 mmol/l. The 4S data are supported by results from the Cholesterol And Recurrent Events (CARE) trial, which has just been published, confirming the 5.2 mmol/l threshold. It demonstrated a significant reduction in the risk of having either fatal coronary heart disease or non-fatal myocardial infarction with treatment by pravastatin in subjects who had a total serum cholesterol <6.2 mmol/l and had had a previous myocardial infarction.

Similarly an impressive prospective primary prevention trial, published in 1995, of cholesterol lowering achieved on pravastatin has been reported by the West Scotland Coronary Prevention Study Group (WOSCPSG).³⁸ After 5 year follow-up of the 6595 male entrants, a 26% lowering of LDL-cholesterol was associated with a 31% reduction in myocardial infarction and mortality, and a 22% reduction in the risk of mortality from any cause, in the pravastatin group. Whether the impressive results from this and the 4S study demonstrate a specific class effect of the 'statins' is unclear, although this is suggested by subsequent analysis of baseline serum cholesterol levels and treatment effect in the 4S study.^{39,40} This demonstrated that there was a reduction in relative cardiovascular risk produced by simvastatin which was independent of baseline lipid levels. Trial data are therefore compelling and support the following priorities for cholesterol-lowering drug treatment (recently endorsed by the European Atherosclerosis Society⁴¹). These include:

1. Aggressive treatment of patients with established coronary heart disease to produce a cholesterol level less than 5.2 mmol/l.
2. Treatment of familial or genetic hyperlipidaemias, or patients with multiple risk factors with cholesterol levels >6.5 mmol/l.
3. Treatment of males with asymptomatic hypercholesterolaemia > 6.5 mmol/l.
4. Treatment of post-menopausal females with hypercholesterolaemia without other risk factors with a cholesterol level >7.8 mmol/l.

The potential importance of lipid-lowering drug therapy in retinovascular disease is shown in the longer-term follow-up of patients with retinal vein occlusion. This approach has suggested that the combined treatment approach of hypertension and hyperlipidaemia, in combination with anti-platelet drug therapy, reduces recurrence in the fellow eye.⁴ Observations in patients with retinal artery occlusion and ischaemic optic neuropathy^{5,13} suggest that these patient groups have a high mortality from coronary artery disease. It would therefore seem appropriate

to treat hyperlipidaemia (hypercholesterolaemia) aggressively, to influence patient survival, particularly in light of the 4S and WOSCPSG studies, and therefore aim to reach a target cholesterol level of 5.2 mmol/l.

Guidance on which class of agent to use is provided by the individual types of hyperlipidaemia. However, in light of the two most recent trials, the HMG CoA-reductase inhibitors (statins) are being more widely used and are well tolerated. New statin agents with increasing lowering effect on triglyceride (VLDL) metabolism will enhance the lipid-lowering effect of this group of agent.

DIABETES MELLITUS

Diabetes mellitus is a frequent medical association with retinovascular disease (retinal vein and retinal artery occlusion, and ischaemic optic neuropathy²). Diabetic retinopathy is a common cause of blindness and severe visual impairment. Recent trials in diabetic patients have shown benefit relevant to both diabetic retinopathy and retinovascular disease.

The first crucial question is 'Does good control of blood glucose influence the microvascular complications of diabetes?' In 1993, the Diabetes Control and Complications Trial Research Group (DCCT) published the results of a 9 year follow-up study of type 1 (insulin-dependent) diabetic patients.⁴² This was a primary and secondary prevention study comparing tight blood glucose control with usual care (mean difference of 2% in glycated haemoglobin between the groups). The main end-point studied was progression of diabetic retinopathy. There was an impressive reduction in both primary and secondary microvascular end-points in the group with tight glucose control, achieving a 76% reduction in the progression of diabetic retinopathy, 33–56% in diabetic nephropathy and 60% in diabetic neuropathic end-points. It has therefore been proven that good glycaemic control does have a major impact on microvascular end-points in type 1 diabetic patients. Although this is a landmark study demonstrating benefit in type 1 diabetic patients, many of those seen with retinopathy are type 2 (non-insulin-dependent) patients with either diabetic maculopathy or retinovascular disease.

The UKPDS trial studying the effects of good diabetic control achieved with different treatment regimens in type 2 diabetes is still to report.⁴³ Whilst we await these results, can the results of the DCCT trial be extrapolated to type 2 diabetic patients? There is no reason to suspect that the benefit to microvascular disease will not equally be applied to type 2 diabetes, whilst noting that type 2 diabetes may have been present for many years before diagnosis, by which time complications may already be established. Caution is also warranted as the least

impressive reduction in the DCCT study was in patients with macular oedema, a pattern most commonly found in type 2 diabetic patients.

Recent surveys of the causes of blindness in diabetic patients have demonstrated changing patterns since the introduction of laser therapy. The ischaemic form of maculopathy is increasing as a cause, being responsible for 48% of the diabetic patients with severe visual impairment, with a similar number developing severe visual impairment due to non-retinopathic causes.²⁸ This latter group includes retinal artery and vein occlusion, and ischaemic optic neuropathy. Considering these latter observations, the DCCT trial has not answered the question of whether improved diabetic control may be beneficial in terms of prevention or progression of ischaemic maculopathy or retinovascular disease.

The importance of hypertension as a risk factor for diabetic retinopathy has recently been realised. Data on treatment of hypertension in diabetic subjects are increasingly showing its importance to retinopathy in type 2 diabetic subjects.^{27,31,44,45} These reports have shown an association of systemic hypertension with retinal exudation and haemorrhage, and other severe forms of diabetic retinopathy. This relationship is strong for both diastolic and systolic hypertension. Treatment of systemic hypertension in association with diabetic retinopathy should therefore have benefit. For example, with advanced retinopathy there is significant capillary damage and leakage, in conjunction with disruption of retinal autoregulation.¹ Clinical trials are suggesting that antihypertensive agents (particularly ACE inhibitors) have a prime role in reducing capillary leakage, and reduce retinal hyperperfusion. There is also the potential to reduce retinal new vessel formation, following the finding that angiotensins 1 to 3 are possible angiogenic growth factors,²⁸ and the advent of angiotensin II receptor antagonist therapy.²⁹

Treatment of the diabetic microvascular complication, nephropathy, has been studied in detail.⁴⁶ Two meta-analyses of trials assessing ACE-inhibitor treatment in diabetics with mild or moderate hypertension, as well as in normotensive diabetic subjects, has demonstrated a reduction in urinary protein excretion (including microalbuminuria) with a reduction in the decline in renal function in predominantly type 1 diabetic nephropathic patients.⁴⁷ One report included in the meta-analysis showed a slowing of the progression of diabetic retinopathy.⁴⁸ Longer-term ACE inhibitor trials with regard to normotensive and hypertensive type 1 and type 2 diabetic subjects are in progress, and data on the progression of diabetic retinopathy will become available. Two publications in 1996 have highlighted the potential reno-protective benefit of ACE inhibitors in hypertensive and normotensive type 2

diabetic patients in randomised controlled studies.^{49,50} The possibility that ACE inhibitors are of value in preventing development of proliferative retinopathy from the pre-proliferative stage is currently being studied. It is therefore widely accepted that ACE inhibitors are the drug of choice in diabetic subjects with hypertension and that diabetes is an indication for aggressive antihypertensive treatment in those with blood pressures above 140 mmHg systolic or 90 mmHg diastolic.

Recent studies have also interestingly highlighted that there may be differences between the drugs comprising the calcium antagonist class, with the suggestion that nifedipine (a dihydropyridine) may increase urinary protein excretion in the presence of diabetic nephropathy in contrast to the non-dihydropyridine group (e.g. diltiazem, verapamil) which may lower urinary protein excretion.⁵¹ Whether this apparent difference is relevant to diabetic retinopathy is unknown.

ANTI-PLATELET AND ANTI-COAGULANT AGENTS

The use of anti-platelet drugs and anti-coagulants should have potential in the management of retinovascular disease.⁵² It has been reliably established that anti-platelet drug therapy reduces the risk of vascular death by about one-sixth and the risk of non-fatal myocardial infarction and stroke by one-third in high-risk patients, as shown in a recent overview of the randomised trials containing 70 000 high-risk patients, and 30 000 low-risk subjects from the general population.⁵³ The reduction in vascular events was by approximately one-quarter in patients with established macrovascular disease (including previous myocardial infarction, acute or previous stroke or transient ischaemic attack, atrial fibrillation, valvular disease, or peripheral vascular disease). The safety of anti-platelet drugs was confirmed by the fact there was no increase in non-vascular deaths in any of the treatment categories. In contrast, low-risk recipients of anti-platelet drug therapy as primary prevention showed a small reduction in non-fatal myocardial infarction but this was accompanied by an increase in stroke end-points (cerebral haemorrhage), such that any clinical benefit would be outweighed by adverse events. The most widely tested regime was aspirin at a dose of 75–325 mg daily. Doses throughout this range seemed similarly effective, and there was no evidence that either a higher dose of aspirin or other anti-platelet regimes was more effective than medium- or low-dose aspirin.

In view of the increased mortality observed in patients with retinal artery or retinal vein occlusion from myocardial infarction and stroke,^{4–6} it would seem appropriate that anti-platelet drug therapy

should therefore have a protective role.^{53–55} Data on longer-term follow-up of patients with retinal vein occlusion using aspirin and/or dipyridamole therapy suggest that the recurrence rate of a retinal venous occlusive event can be significantly reduced.⁴

The role of thrombolytic agents has been precisely defined with definite clinical indications in the 1990s, such that streptokinase and tissue plasminogen activator have assumed a central role in the management of acute coronary artery disease.^{56,57} However, evidence that this might be of benefit to patients with retinovascular disease is limited. Anecdotal reports have suggested that streptokinase may be of benefit in acute episodes of retinal artery occlusion with reperfusion. However, these agents have to be given within a few hours of the occlusive event. This gives rise to difficulty in patients with retinovascular disease as many patients do not present to medical services acutely. However, a formal randomised trial using streptokinase has been proposed in patients with acute retinal artery occlusion.

In patients with completed central retinal vein occlusion, early studies using streptokinase showed an overall deterioration in retinal changes due to increasing haemorrhage, with reduction in visual acuity.⁵⁸ However, thrombolytic therapy could have a role in patients with incipient central retinal vein occlusion, though the delay common in the presentation of patients to clinical services may again create difficulties.

ATHEROMATOUS CAROTID DISEASE

Many patients with transient ischaemic attacks, amaurosis fugax, branch retinal artery occlusion and ischaemic optic neuropathy, have evidence of atheromatous carotid disease on duplex scanning. These associations have been confirmed in previous studies using carotid angiography.⁵⁹ In the 1980s, a consensus view was that the benefits of carotid endarterectomy were limited in female patients because of the high peri-operative risks, particularly with regard to stroke. In contrast, in males, there was evidence of benefit of this procedure which outweighed the significant peri-operative complication rate.⁶⁰

However, this view has changed following the reports of several large studies in the 1990s. These include the European Carotid Surgery Trial incorporating 778 patients and the North American Symptomatic Carotid Endarterectomy Trial. These two studies have established definite clinical benefit of carotid endarterectomy in reducing subsequent stroke rate in patients with severe carotid stenosis (a 70–99% reduction in carotid artery diameter) in association with recent symptoms of cerebrovascular disease arising from the carotid artery territory. The value of treatment was shown by the reduction in

stroke rate from 22% to 12.3% by surgical intervention; these figures included all surgical risks. Carotid surgery trials included patients up to, and even over, the age of 80 years, provided they were otherwise medically fit. Recent myocardial infarction, unstable angina or poorly controlled hypertension were reported as contraindications to investigation and subsequent surgery.

Clinical practice in the 1990s has therefore changed in that patients who are fit for anaesthesia, irrespective of age, who have transient ischaemic attacks, amaurosis fugax, or minor or major ischaemic strokes arising from the carotid artery territory and who have made a good recovery within 6 months, should be investigated for carotid stenosis as well as for cardiovascular risk factors.⁶¹ Although benefit has been clearly demonstrated in those patients with a carotid stenosis >70%, the benefit of surgery in patients with stenosis <70% is unclear.⁶⁰

The implications of these findings for patients with retinal arterial disease are that, irrespective of age, duplex scanning of the carotid should be performed, and carotid surgery considered if a stenosis >70% is discovered. Whether a more aggressive approach towards treatment of other coexisting risk factors, namely hypertension, hyperlipidaemia, smoking and diabetes, will prevent progression of carotid atheromatous vascular disease remains speculative, although early data on lipid-lowering therapy with simvastatin have shown a tendency to a delay in atheromatous progression of carotid stenosis.⁶² Aspirin should be started as soon as possible before carotid surgery is considered and continued indefinitely.⁶¹

OTHERS INTERVENTIONS

Hormone Replacement Therapy

Owing to widespread concerns about the possible balance of the risks and benefits of exogenous oestrogen therapy, currently only 12% of post-menopausal women in the UK receive hormone replacement therapy (HRT). Many of the concerns result from an inappropriate comparison of the adverse effects of the combined oral contraceptives and the known risks of high-dose synthetic oestrogen formulations, with the lower replacement dosages of the natural mammalian oestrogens used in HRT. HRT can be of major benefit to patients in terms of relieving acute menopausal symptoms, preventing deterioration in the ageing tissues of the vagina and urethra, and preventing osteoporosis.^{63,64}

Normal ovarian activity is also protective against coronary artery disease, but this steadily reduces after the menopause.⁶⁴ Premature loss of ovarian function is an established risk factor for heart disease in females, and many observational studies with HRT suggest this risk can be reduced by about

50%.⁶⁵⁻⁶⁷ This was well demonstrated in the largest prospective cohort study in the United States, in which 48 470 nurses were followed for a total of 337 854 woman-years.⁶⁶ In the current users of HRT in this study, the relative risk of major ischaemic heart disease adjusted for age and other risk factors was 0.6, which was significantly lower than for patients who had never used HRT. A recent review concluded that the incidence of ischaemic heart disease is reduced in HRT users by 20%, and that of stroke by 15%. However, there are no prospective randomised studies to confirm the observational reports.

The medical management in the 1980s of a patient on HRT who had a retinovascular occlusion was to discontinue HRT. There are several anecdotal and single case reports of patients on HRT, or the combined oral contraceptive pill, who developed retinovascular disease implicating HRT as an aetiological factor.² It is now established from recent studies that these two therapies should be considered separately.⁶⁶⁻⁶⁸

Patients on the combined oral contraceptive pill should have this discontinued in the presence of a retinal artery or retinal vein occlusion, as failure to do so can lead to recurrence in the fellow eye with a potentially disastrous visual outcome.² With increasing use of HRT, a number of patients with retinovascular disease will also be on this therapy, but on detailed medical investigation other known cardiovascular risk factors are usually identified. In view of the increased morbidity of patients with retinovascular disease from ischaemic heart disease and stroke, appropriate management should be to continue natural formulations of HRT which could be of benefit with regard to macrovascular disease. Recent data support this approach, with no increase in blood pressure being reported in hypertensive patients taking HRT.⁶⁹

Smoking

The relationship of smoking with retinovascular disease and diabetic retinopathy has been studied extensively. The results with regard to diabetic retinopathy are inconclusive although smoking would not be recommended in view of the high prevalence of large vessel disease associated with diabetes mellitus. Smoking does strongly relate to, and is predictive of, retinal arterial occlusive disease, but the association is weaker for retinal venous disease.² Current management of patients with retinovascular disease is to discontinue smoking, but there is no longer-term study showing this sole intervention to be of benefit in the context of diabetic retinopathy or retinovascular disease.

A recent overview and meta-analysis of therapies that are available for smoking cessation has recently

been published.⁷⁰ Nicotine replacement therapy by gum, transdermal patch or intra-nasal spray has been tested in 53 trials. The use of nicotine replacement did increase the ratio of abstinence (odds ratio 1.71) compared with those allocated to control interventions. The best abstinence rate was seen for inhaled nicotine, and the lowest rate with nicotine chewing gum.

CONCLUSION

The many recent, large prospective trials of the treatment of cardiovascular risk factors have shown major benefit, with reduction of macrovascular disease end-points. The inference from these trials for medical ophthalmology practice (with particular reference to retinovascular disorders) is that aggressive treatment should be undertaken with attention to underlying cardiovascular risk factors. The potential to reduce macrovascular end-points, increase survival and reduce visual impairment in patients with retinovascular disease has become increasingly clear from the trial results. Once a diagnosis of retinovascular disease is made, detailed and expert ophthalmological and medical investigation and supervision should not be denied to patients, to maximise the potential benefits from currently available and proven therapies.

REFERENCES

1. Kohner EM. Diabetic retinopathy. *BMJ* 1993;307:1195-9.
2. Dodson PM, Gibson JM, Kritzinger EE. Clinical retinopathies. London: Chapman and Hall, 1995.
3. Dodson PM, Kritzinger EE, Clough CG. Diabetes mellitus and retinal vein occlusion in patients of Asian, West Indian and White European origin. *Eye* 1992;6:66-8.
4. Tsaloumas MD, Kirwan K, Gilleran G, Vinall H, Prior P, Kritzinger EE, Dodson PM. A large cohort study of morbidity and mortality in retinal vein occlusion: two thousand 900 years of follow-up. Proceedings of the Annual Congress of College of Ophthalmologists 1995:48.
5. Hankey GJ, Slattery JM, Warlow CP. Prognosis and prognostic factors of retinal infarction: a prospective cohort study. *BMJ* 1991;302:499-504.
6. Rubinstein K, Jones EB. Retinal vein occlusion: long term prospects. Ten years follow-up of 143 patients. *Br J Ophthalmol* 1976;60:145-50.
7. Howard RS, Ross Russell RW. Prognosis of patients with retinal embolism. *J Neurol Neurosurg Psychiatry* 1987;50:1142-7.
8. Glacet-Bernard A, Coscas G, Chabanel A, *et al.* Prognostic factors for retinal vein occlusion. *Ophthalmology* 1996;103:551-60.
9. Hayreh SS, Zimmermann MB, Podhajsky P. Incidence of various types of retinal vein occlusion and their recurrence and demographic characteristics. *Am J Ophthalmol* 1994;117:429-41.
10. Dodson PM, Kritzinger EE. Management of retinal vein occlusion. *BMJ* 1987;295:1434-5.
11. Dodson PM, Kubicki AJ, Taylor KG, Kritzinger EE.

- Medical conditions underlying recurrence of retinal vein occlusion. *Br J Ophthalmol* 1985;69:493-6.
12. Talks SJ, Chong NHV, Gibson JM, Dodson PM. Fibrinogen, cholesterol and smoking as risk factors for non-arteritic anterior ischaemic optic neuropathy. *Eye* 1995;9:85-8.
 13. Beri M, Klugman MR, Kohler JA, Hayreh SS. Anterior ischaemic optic neuropathy. VII. Incidence of bilaterality and various influencing factors. *Ophthalmology* 1987;94:1020-8.
 14. Barnett AH, Dodson PM. Hypertension and diabetes. 2nd ed. London: Science Press, 1996.
 15. Collins R. Hypertension treatment trials: update meta-analysis. *Br Med Bull* 1994;52:272-90.
 16. The Systolic Pressure in the Elderly Program Co-operative Research Group. Implications of the Systolic Pressure in the Elderly Program. *Hypertension* 1993; 21:335-43.
 17. Dahlof B, Lindholm LH, Hansson L, Schersten B, Ekbom T, Webster PO. Morbidity and mortality in the Swedish trial in older patients with hypertension. *Lancet* 1991;338:245-50.
 18. Bulpitt CJ. Shall we treat isolated systolic hypertension in 1994? *J Hum Hypertens* 1994;8:785-8.
 19. Sever P, Beevers G, Bulpitt C, *et al.* Management guidelines in essential hypertension: report of the second working party of the British Hypertension Society. *BMJ* 1993;306:983-7.
 20. Subcommittee of WHO/ISH Mild Hypertension Liaison Committee. Summary of the 1993 World Health Organization/International Society of Hypertension guidelines for management of mild hypertension. *BMJ* 1993;307:1541-6.
 21. Dodson PM, Lip GYH, Eames SM, Gibson JM, Beevers DG. Hypertensive retinopathy: a review of existing classification systems and a suggestion for a simplified grading system. *J Hum Hypertens* 1996;10:93-8.
 22. Conway J, *et al.* The use of ambulatory blood pressure monitoring to improve the accuracy and reduce the number of subjects in clinical trials of anti-hypertensive agents. *J Hum Hypertens* 1988;6:111-6.
 23. Padfield PL, Benediktsson R. Ambulatory blood pressure monitoring: from research to clinical practice. *J Hum Hypertens* 1995;9:413-6.
 24. Verdecchia P, *et al.* Circadian blood pressure change and left ventricular hypertrophy in essential hypertension. *Circulation* 1990;81:528-36.
 25. Slovick DI, Amery A, Birkenhager W, Bulpitt CJ, *et al.* SYST-EUR multicentre trial on the treatment of isolated systolic hypertension in the elderly: first interim report. *J Hum Hypertens* 1993;7:201-3.
 26. Hayreh SS. Systemic arterial blood pressure and the eye. *Eye* 1996;10:5-28.
 27. Parving HH, Larsen M, Mominel E, Lund-Andersen H. The effect of anti-hypertensive treatment on blood-retinal barrier permeability in hypertensive type I (insulin-dependent) diabetic patients with background retinopathy. *Diabetologia* 1989;32:440-4.
 28. Eames SM, Dodson PM. Treatment of diabetic retinopathy. *Diabetes Rev* 1994;3:5-9.
 29. Timmermans PB, Wong PC, Chice AT, Herblin WF, Smith RD. New perspectives in angiotensin system control. *J Hum Hypertens* 1993;7(Suppl 2):S19-31.
 30. Winder AF, Dodson PM, Galton DJ. Ophthalmological complications of hypertriglyceridaemia. *Trans Ophthalmol Soc UK* 1980;100:119-22.
 31. Dodson PM, Gibson JM. Long-term follow-up and underlying medical conditions in patients with diabetic exudative maculopathy. *Eye* 1991;5:699-703.
 32. Gordon B, Chang S, Kavanagh M, Barocal M, Yannuzzi L, Robertson C, Drexler A. The effects of lipid lowering on diabetic retinopathy. *Am J Ophthalmol* 1991;112:385-91.
 33. Betteridge DJ, Dodson PM, Durrington PN, *et al.* Management of hyperlipidaemia: guidelines of the British Hyperlipidaemia Association. *Prostagrad Med J* 1993;69:359-69.
 34. Law MR, Wald NJ, Thompson SG. By how much and how quickly does reduction in serum cholesterol concentration lower risk of ischaemic heart disease. *BMJ* 1994;308:367-72.
 35. Law MR, Thompson SG, Wald NJ. Assessing possible hazards of reducing serum cholesterol. *BMJ* 1994;308:373-9.
 36. Muldoon MF, Manuck SB, Matthews KA. Lowering cholesterol concentrations and mortality: a quantitative review of primary prevention trials. *BMJ* 1990;301:309-13.
 37. The Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994;344: 1383-9.
 38. Shepherd J, Cobbe SM, For I, *et al.* Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *N Engl J Med* 1995;333:1301-7.
 39. Scandinavian Simvastatin Survival Study Group. Baseline serum cholesterol and treatment effect in the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1995;345:1274-5.
 40. Massy ZA, Keane WF, Kasiske BL. Inhibition of the mevalonate pathway: benefits beyond cholesterol reduction? *Lancet* 1996;347:102-3.
 41. Recommendations of the European Atherosclerosis Society. Prevention of coronary heart disease: scientific background and new clinical guidelines. *Nutr Metab Cardiovasc Dis* 1992;2:113-56.
 42. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993;329:977-1036.
 43. UK Prospective Diabetes Study Group. UK Prospective Diabetes Study (UKPDS). VIII. Study design, progress and performance. *Diabetologia* 1991;34: 877-90.
 44. Klein R, *et al.* The Wisconsin Epidemiologic Study of Diabetic Retinopathy. III. Prevalence and risk factors of diabetic retinopathy when age at diagnosis is 30 or more years. *Arch Ophthalmol* 1984;102:527-32.
 45. Cignarelli M, *et al.* High systolic blood pressure increases prevalence and severity of retinopathy in NIDDM patients. *Diabetes Care* 1992;15:1002-8.
 46. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD. The effect of angiotensin converting enzyme inhibition on diabetic nephropathy. *N Engl J Med* 1993;329:1456-62.
 47. Kasiske BL, *et al.* Effect of antihypertensive therapy on the kidney in patients with diabetes: a meta-regression analysis. *Ann Intern Med* 1993;118:129-38.
 48. Ravid M, *et al.* Long term stabilising effect of angiotensin converting enzyme inhibition on plasma creatinine and on proteinuria in normotensive type 2 diabetic patients. *Ann Intern Med* 1993;118:557-81.
 49. Sano T, Motta N, Kawamura T, *et al.* Effects of long term enalapril treatment on persistent microalbuminuria in normotensive type 2 diabetic patients: results

- of a 4-year prospective randomised study. *Diab Med* 1996;13:120-4.
50. Agardh CD, Garcia-Puig J, Charbonnel B, Angelkort B, Barnett AH. Greater reduction of urinary albumin excretion in hypertensive type 2 diabetic patients with incipient nephropathy by lisinopril than by nifedipine. *J Hum Hypertens* 1996;10:185-92.
51. Bakris GL, Barnhill BW, Sadler R. Treatment of arterial hypertension in diabetic humans: importance of therapeutic selection. *Kidney Int* 1992;41:912-9.
52. Orme M. Aspirin all around. *BMJ* 1988;297:307-8.
53. Antiplatelet Trialist Collaboration. Collaborative overview of randomised trials of anti-platelet therapy. I. Prevention of death, myocardial infarction and stroke by prolonged anti-platelet therapy in various categories of patients. *BMJ* 1994;308:81-106.
54. Dodson PM, Gill J, Clough C, Kritzing EE. Are retinal vein occlusion and cerebral infarction related? *Proceedings of Annual Congress of the College of Ophthalmologists* 1993:93.
55. Multicentre Acute Stroke Trial: Italy (MAST-1) Group. Randomised controlled trial of streptokinase, aspirin, and combination of both in treatment of acute ischaemic stroke. *Lancet* 1995;346:1509-14.
56. The Gusto Investigators. An international randomised trial comparing four thrombolytic strategies for acute myocardial infarction. *N Engl J Med* 1993;329:673-82.
57. Di-Salvo TG, Fuster V. Antithrombotic therapy in coronary artery disease. *Curr Opin Lipidol* 1994;5: 290-304.
58. Kohnert EM, Petit JE, Hamilton AM, Bulpitt CJ, Dollery CT. Streptokinase in central retinal vein occlusion: a controlled clinical trial. *BMJ* 1976;1:550-3.
59. Wilson LA, Warlow CP, Ross Russell RW. Cardiovascular disease in patients with retinal arterial occlusion. *Lancet* 1979;1:292-4.
60. Murie JA, Morris PJ. Carotid endarterectomy in Great Britain and Ireland. *Br J Surg* 1986;76:867-70.
61. Brown MM, Humphrey PRD. Carotid endarterectomy: recommendations for management of transient ischaemic attack and ischaemic stroke. *BMJ* 1992;305:1071-4.
62. Crouse JR, Byington RP, Bond MG. Pravastatin, lipids and atherosclerosis in the carotid arteries (LAC-11). *Am J Cardiol* 1995;75: 455-9.
63. Nabulsi AA, Folsom AR, White A, *et al.* Association of hormone replacement therapy with various cardiovascular risk factors in post-menopausal women. The Atherosclerosis Risk in Communities Study Investigators. *N Engl J Med* 1993;328:1069-75.
64. Christiansen C, Christiansen MS, Transbol I. Bone mass in post-menopausal women after withdrawal of oestrogen/gestagen replacement therapy. *Lancet* 1981;1:459-61.
65. Stampfer MJ, Colditz GA. Estrogen replacement therapy and coronary heart disease: a quantitative assessment of the epidemiologic evidence. *Prev Med* 1991;20:47-63.
66. Stampfer MJ, Colditz GA, Willett WC. Postmenopausal oestrogen therapy and cardiovascular disease: ten-year follow-up from the nurses health study. *N Engl J Med* 1991;325:756-62.
67. Meade TW, Berra A. Hormone replacement therapy and cardiovascular disease. *Br Med Bull* 1992;48: 276-308.
68. Kirwan JF, Tsaloumas MD, Vinall H, Prior P, Kritzing EE, Dodson PM. Sex hormone preparations and retinal vein occlusion. *Eye* 1997;11:53-6.
69. Lip GYH, Beevers M, Churchsill D, Beevers G. Hormone replacement therapy and blood pressure in hypertensive women. *J Hum Hypertens* 1994;8:491-4.
70. Silagy C, Mant D, Fowler G, Lodge M. Meta-analysis on efficacy of nicotine replacement therapies in smoking cessation. *Lancet* 1994;343:139-42.