Nine year follow-up study of morbidity and mortality in retinal vein occlusion

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Abstract

Purpose **The aim of this study was to conduct a detailed retrospective follow-up of a large cohort of patients with retinal vein occlusion (RVO), examining morbidity and mortality, to investigate a possible relationship between RVO, large vessel disease and stroke, and to determine whether recurrence of RVO was influenced by treatment of associated medical conditions.**

Methods **A follow-up study was undertaken in 1994 of all patients (n = 588) who presented to the medical ophthalmology clinics of the Birmingham and Midland Eye Hospital between 1982 and 1989 with a definitive diagnosis of RVO.**

Results **Follow-up data were obtained on 549 patients (93%). Results showed that recurrence of RVO in the same or fellow eye was decreased by more than half in the follow-up group (3.3%) when compared with the known recurrence rate at initial presentation (8.8%). Comparison of the deceased with the survivors showed that the deceased patients were significantly older (mean age 70.2 vs 63.4 years). The prevalence of rubeosis iridis and smoking were statistically significantly increased when comparing the deceased with the survivors ($p < 0.016$ and $p < 0.008$ respectively). The deceased had a higher prevalence of diabetes (15.8% vs 10.1%), and there was a trend towards increased clinically evident macrovascular disease in those patients who had died (23.2% vs 19.5%). Neither hypertension nor hyperlipidaemia predicted death, as the prevalence rates of the two conditions were similar in survivors and those who had died (60.0% vs 60.6% and 48.4% vs 53.3%). The percentage of patients taking antiplatelet drug therapy was not different in the two groups (36.8% vs 38.3%). Analysis of the causes of death of the RVO population (n = 95) compared with the causes of death in the West Midlands population as a whole, showed that the percentage of deaths from myocardial infarction in the RVO population was significantly higher (23.1% vs 14.4%, $p < 0.05$). There was no statistical difference between the populations for ischaemic heart disease and stroke, although there was a trend for increased mortality from stroke (19% vs 13.5%).**

Conclusion **These data suggest a relationship between RVO, mortality and increased cardiovascular risk factors (smoking, diabetes and macrovascular disease), and support the possibility of an association between RVO and stroke. They also support the potential value of medical treatment of underlying medical conditions in preventing recurrence of RVO.**

Key words Retinal vein occlusion, Morbidity, Mortality

Retinal vein occlusion (RVO) is an established cause of visual loss in the middle-aged and elderly population. Studies have identified major medical conditions associated with RVO, such as hypertension, hyperlipidaemia and diabetes mellitus,[1–3] although the extent to which these various factors contribute varies in different studies.[4–6] Conditions also implicated in the aetiology include vasculitis and hyperviscosity syndrome.[7,8] Hyperlipidaemia has been implicated as the predominant associated medical condition in younger patients (< 50 years),[9] and more recently activated protein C resistance.[10] Patients with recurrent RVO have been found to have an even higher prevalence of systemic hypertension, poor control of hypertension, and an increase in the prevalence of hyperlipidaemia.[11]

In one histological study retinal artery abnormalities were observed to accompany branch retinal vein occlusion,[12] and the observation that retinal artery occlusion and RVO can occur in the same patient[13] gives rise to the debate that retinal artery disease may be linked to RVO. This is supported by evidence of branch RVO occurring at the site of arteriovenous crossings,[14,15] and the fact that similar cardiovascular risk factors can underlie both retinal artery and retinal vein occlusion.[16,17] If retinal arterial disease has an aetiological role in RVO it could be anticipated that they may have a similar outcome in terms of cardiovascular morbidity and mortality. It is

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of interest in this context, therefore, that patients with retinal artery occlusion have been shown to have an increased mortality from coronary events rather than stroke.[18] In contrast a previous (but incomplete) follow-up study in patients with RVO suggested that both cerebral and cardiac vascular causes of death were predominant.[19] In that study only 143 of 226 (63%) patients were traceable for follow-up, leaving a large percentage of patients unrecorded, and making interpretation of the results difficult.

The aim of this study, therefore, was to conduct a detailed complete long-term follow-up of a large cohort of patients with RVO, examining morbidity and mortality. Since the major medical conditions associated with RVO also predispose to macrovascular disease such as myocardial infarction (MI), ischaemic heart disease (IHD) and stroke (CVA), we have studied possible relationships between RVO, large vessel disease, stroke and cancer rates over long-term follow-up. A further aim was to determine whether treatment of associated medical conditions influences the recurrence of RVO.

Method

Five hundred and eighty-eight sequential patients who presented to the Birmingham and Midland Eye Hospital between 1982 and 1989 with a definitive diagnosis of RVO were restudied in 1994 with a follow-up period from 1 to 12 years (mean follow-up 9.08 years). The initial diagnosis of RVO was made on clinical history and fundoscopy and, in equivocal cases, confirmed by fluorescein angiography. All patients had, at initial presentation to the medical ophthalmology clinic, extensive ophthalmic and medical assessment. Hypertension was defined according to WHO criteria and hyperlipidaemia was defined according to the criteria of the British Hyperlipidaemic Association.[20,21]

Medical treatment of underlying conditions such as hypertension and hyperlipidaemia was instituted by the examining physician (P.M.D.).[2,22] Hyperlipidaemia was treated by a standard dietary approach but a small proportion of patients required lipid-lowering drug therapy. Antiplatelet treatment, aspirin, persantin or both was instituted when the visual outcome was poor (6/36 Snellen visual acuity or less) and if the vein occlusion was deemed to be a recurrence at the time of initial presentation to the clinic. Ophthalmic management was based on clinical findings, and laser treatment given in accordance with the findings of previous studies.[23–25] Details of the original data collected and the management scheme have been published elsewhere.[22]

Follow-up data were by review of hospital records and clinic visits up to December 1994, from death certificates, and by a questionnaire sent to all patients. In the letter questions were aimed at establishing whether patients who had been discharged or had no recent (within 12 months) outpatient attendance had developed new clinical conditions since their last clinic visit. The questionnaire asked in lay terms specific questions about transient ischaemic attacks and stroke, hypertension, angina and myocardial infarction, hyperlipidaemia and diabetes, surgical procedures and cancer. The patients were also asked about their current alcohol and smoking habits, drug therapy and whether they had had ocular symptoms, particularly sudden loss of vision suggestive of a recurrence of vein occlusion, particularly in the fellow eye.

In 215 cases (39.2%), data were obtained from hospital records and current clinic visits, and in 239 cases (43.5%) from hospital record supported by the questionnaire. Ninety-five patients (17.3%) died during the follow-up period.

In those instances where the patient had died, the cause of death was obtained from hospital records and death certificates searches, both regional and national. When more than one cause of death was listed on the death certificate the primary cause of death was recorded.

Rubeosis data were compiled while the patient was still under review in the ophthalmic clinic. All patients (except where death intervened) were kept under ophthalmic and medical review for at least 2 years after the occurrence of RVO. In those cases where the patient underwent laser treatment, review was continued for a minimum of 2 years after the last episode of treatment. Patients with persistent medical problems or coexistent ocular problems were kept under long-term review.

Death statistics for the West Midlands population as a whole for 1992 were obtained from the Office of Population Censuses and Surveys (OPCS).[26] A life table was constructed for the period from occurrence of RVO to death (the primary end-point) or end of census (December 1994). All data were coded onto SPSS (Statistical Package for Social Services, version 6.1) for Windows. Descriptive statistics using unpaired *t*-test, chi-squared tests as well as univariate analysis statistics were undertaken.

Hospital ethics committee approval was obtained.

Results

Of the 588 sequential patients in the original study, 39 were not traceable for follow-up. Follow-up data were therefore obtained on 549 patients (93%), coded onto a protocol and incorporated with the original data collected. The mean follow-up period for the whole group was 9.08 (range 1–12 years). Ninety-five patients (17.3%) had died in the follow-up period and the cause of death was undetermined in 6 cases. The clinical details of the patients in the follow-up group are shown in Table 1.

Of the original 588 patients who presented to the Birmingham and Midland Eye Hospital between 1982 and 1989, 49 (8.3%) presented with a recurrent RVO, in either the same eye or the fellow eye, on first referral to our clinic and hence initial inclusion into the study. During the follow-up period ranging from 1 to 12 years there were 18 new recurrences (3.3%) of RVO in patients who on first inclusion into the study had had only one episode of RVO as shown in Table 1. The occurrence of

Table 1. *Clinical details of patients in the follow-up group* (n = 549)

Parameter	Number	Percentage
Mean age (years)		
CRVO	64.6 (SD 14.22)	
BRVO	63.76 (SD 11.73)	
Age range (years)	23–92	
Male:Female ratio[a]	286:250	52.1:45.5
Ethnic groups:		
Caucasians	497	90.5
West Indian	24	3.8
Asian	28	4.6
Type of RVO (n = 549)		
CRVO	261	47.5
BRVO	288	52.5
New recurrences	18	3.3

[a]Thirteen patients were not coded for sex.
CRVO, central retinal vein occlusion; BRVO, branch retinal vein occlusion; RVO, retinal vein occlusion.

Table 2. *New medical conditions at the end of the follow-up period compared with those diagnosed at initial presentation*

Parameter	Data at presentation (n = 588)	Data at end of follow-up (n = 549)	New diagnoses
Diabetes	55	70	15
TIA	3	19	16
CVA	19	29	10
Angina	24	34	10
MI	18	29	11
Hypertension			
Established	172	172	
New	145	160	15
Hyperlipidaemia	265	288	23
Use of antiplatelet drugs	–	209	–
Malignancies		31	
Current smoker	149	145	–4
Alcohol	363	325	–38
Recurrence of RVO	49	67	18

TIA, transient ischaemic attack; CVA, cerebrovascular accident; MI, myocardial infarction; RVO, retinal vein occlusion.

new medical conditions diagnosed during the follow-up period compared with the original data set is also shown in Table 2.

Table 3 compares the deceased patients (n = 95, 17.3%) with those alive (n = 454) at the end of the follow-up. The prevalence of underlying medical conditions, the presence of rubeosis, smoking habits and usage of antiplatelet therapy are compared. Comparison of the deceased with the survivors showed that the deceased patients were significantly older (mean age 70.2 vs 63.4 years, $p < 0.001$). The age range of the deceased patients was 39–92 years, which was not significantly different from that of the surviving patients of (23–88 years). Rubeosis and smoking were statistically significantly increased when comparing the deceased with the survivors. Rubeosis as a significant risk factor was not influenced by age (67.3 vs 64.6 years, $p = 0.113$), with the majority of patients with rubeosis having suffered a central RVO (CRVO) rather than a branch RVO (BRVO) (47 vs 3). The deceased had a trend to an increased prevalence of diabetes (15.8% vs 10.1%).

There was also a trend towards clinically evident macrovascular disease in those patients who had died (23.2% vs 19.5%). Hypertension and hyperlipidaemia prevalence rates were similar in those who had died versus those who were alive. There was no increase in recurrence of occlusion in those who died and there was no statistical difference in the type of venous occlusion (CRVO vs BRVO).

The time of death after occurrence of RVO and the cause of death in the 95 patients who had died in the follow-up period were determined. There was no peak time of death after occurrence of venous occlusion, and no significant difference between BRVO and CRVO with regard to time of death, with over 50% of deaths occurring in the first 6 years (Fig. 1). A survival curve for the RVO population is depicted in Fig. 2. The major causes of death were myocardial infarction, ischaemic heart disease, cerebrovascular accident and malignancy (Table 4). Malignancy as a cause of death was more commonly associated with CRVO rather than BRVO, but there were no other notable differences in causes of death

Table 3. *Characteristics of the deceased population versus survivors at follow-up*

	Patients deceased (n = 95)		Patients alive (n = 454)		
Variable	Number	Percentage	Number	Percentage	p value
Mean age	70.2		63.4		<0.0001
Diabetes	15	15.8	55	10.1	NS
Previous MI	8	8.4	21	4.6	NS
Angina	9	9.5	25	5.5	NS
TIA	2	2.1	17	3.7	NS
Previous CVA	3	3.2	26	5.7	NS
Hypertension	57	60	275	60.6	NS
Hyperlipidaemia	46	48.4	242	53.3	NS
Rubeosis iridis	14	14.7	38	8.4	<0.016
Smoker	33	34.7	112	24.7	<0.008
Antiplatelet drugs	35	36.8	242	38.3	NS
Recurrence of RVO	3	3.2	15	3.3	NS
CRVO	50	52.6	211	46.5	NS
BRVO	45	47.3	243	53.5	NS

TIA, transient ischaemic attack; CVA, cerebrovascular accident; MI, myocardial infarction; CRVO, central retinal vein occlusion; BRVO, branch retinal vein occlusion.

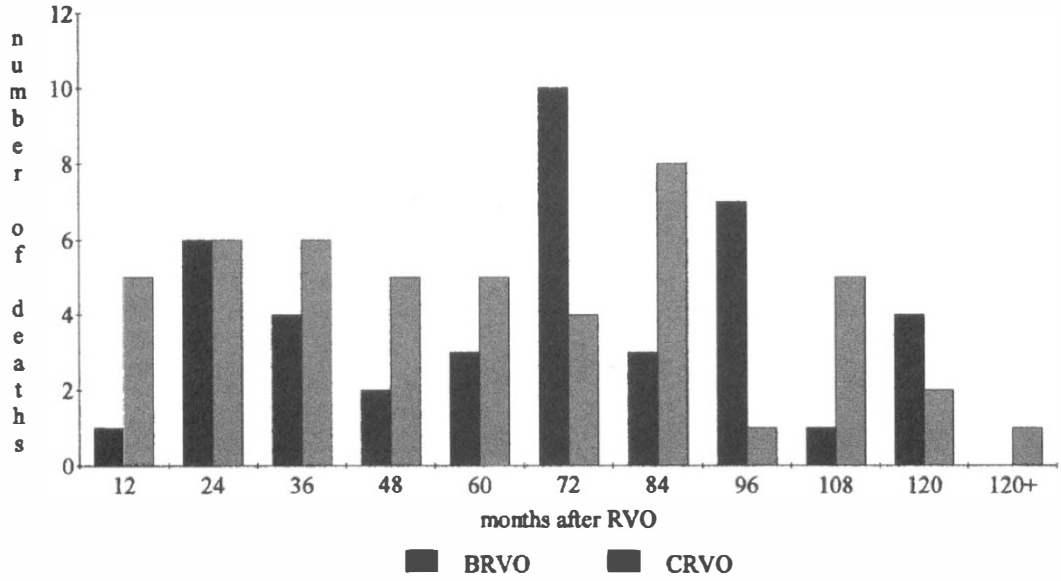

Fig. 1. *Number of months from occurrence of RVO to death.*

between the two types of RVO. To assess whether the RVO population had an excess death rate from particular causes, we compared the causes of death in our study population against those of the West Midland population,[26] with data recorded for 1992 in the 23–92 years age group, which was the age range of the patients in this study as shown in Table 5.

Myocardial infarction was a statistically increased cause of death in RVO patients compared with the West Midland population, whereas malignancy was significantly lower ($p< 0.05$; Table 5). There was no statistical difference between the populations in the rates of ischaemic heart disease and cerebrovascular accident, although there was a trend towards a greater number of deaths from cerebrovascular accident in the RVO population.

Discussion

This study is a large retrospective study looking at the long-term medical outcome of patients with RVO, who have been extensively investigated and given appropriate treatment (according to guidelines available in the 1980s) of underlying medical conditions diagnosed at presentation of venous occlusion. This study does not report a randomized treatment trial, which would not now be ethical to perform in the context of RVO, owing to the proven benefit of medical treatment of hypertension and hyperlipidaemia irrespective of the occurrence of RVO. This study design was therefore one of the few options open to provide useful data on this topic.

A number of major findings are highlighted in this study. These are firstly that hypertension, hyperlipidaemia and diabetes are confirmed as

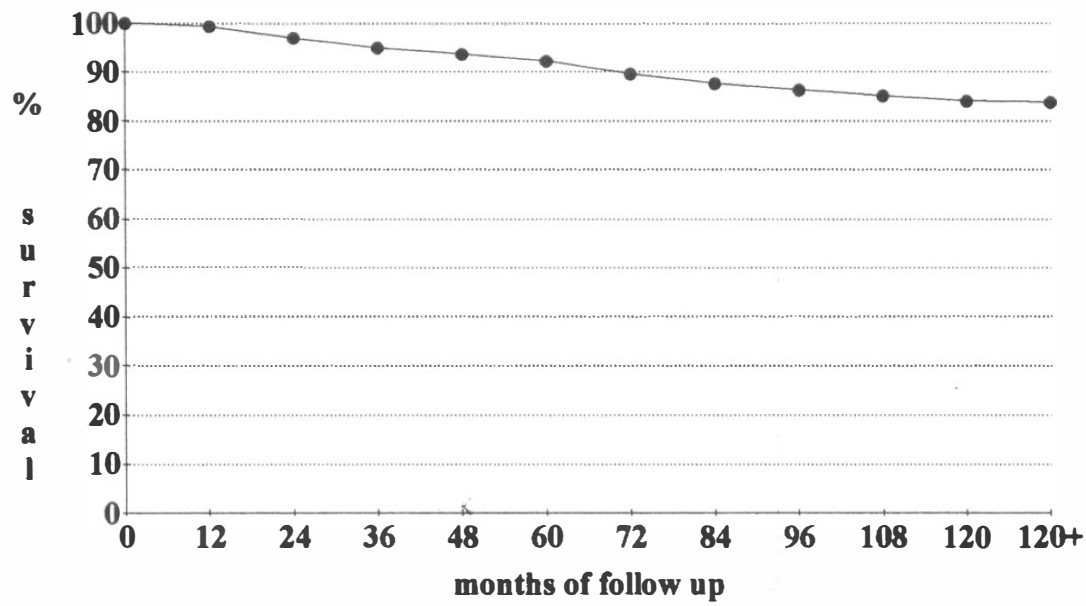

Fig. 2. *Survival curve for patients with retinal vein occlusion* (n = *89 known causes and times of death).*

Table 4. *Causes of death in 95 patients with RVO who died in the follow-up period*

Cause of death	Total group (n = 95) Number	Percentage	BRVO (n = 45)	CRVO (n = 50)
Myocardial infarction	22	23.1	13	9
Ischaemic heart disease	19	23	10	9
CVA	18	18.9	10	8
Malignancy	16	16.8	5	11
Bronchopneumonia	3	3.1	1	2
Other	11	11.6	2	9
Not known	6	6.3	4	2

CVA, cerebrovascular accident.

important underlying conditions. Secondly that the recurrence rate of RVO was halved in the follow-up period. Thirdly, rubeosis and smoking were statistically significantly increased when comparing the deceased with the survivors, and the deceased had a higher prevalence of diabetes. Fourthly, analysis of the causes of death of the RVO population compared with the causes of death in the West Midlands population as a whole, showed that the percentage of deaths from myocardial infarction in the RVO population was significantly higher.

The results from our study support various observations from previous reports which will now be outlined. Hypertension, hyperlipidaemia and diabetes are confirmed as important underlying risk factors for RVO.[1–6] The relatively small number of new cases diagnosed in the follow-up period would suggest that most underlying conditions were diagnosed at first presentation.

Recurrent RVO has been shown to be associated with an increased prevalence of hypertension and a tendency to increased hyperlipidaemia and regular alcohol intake.[11] In our original group of patients, 49 patients (8.3%) already had a recurrent RVO on first presentation and inclusion into the study. In our long-term follow-up period only a further 18 patients (3.3%) suffered a recurrent occlusion, with a recurrence rate that was more than halved, suggesting that medical intervention may be of benefit. This is further supported by the fact that our recurrence rate (3.3%) was markedly lower than the 14.4% found by Hayreh *et al.*[27] within 4 years of presentation of RVO, which represents only half the period of our follow-up.

Table 5. *Causes of death in the retinal vein occlusion study group compared with the causes of death in the West Midlands population for 1992*

Cause of death	% RVO population	% West Midlands population
MI	23.1	14.39*
IHD	20	26.37
CVA	18.9	13.50
Malignancy	16.8	26.14*

MI, myocardial infarction; IHD, ischaemic heart disease; CVA, cerebrovascular accident.
*$p < 0.05$.

All patients in the original study group had received appropriate treatment for underlying medical conditions such as hypertension, diabetes and hyperlipidaemia, as well as counselling on reducing alcohol intake and cessation of smoking. These results would suggest, therefore, that treatment of underlying medical conditions in patients may indeed reduce the recurrence rate in the same or fellow eye and hence avoid a potentially disastrous visual outcome. Recurrence of RVO did not predict mortality, as shown by the similar percentages of recurrences in the deceased group compared with the survivors.

A potential source of error in our study with regard to recurrence of RVO should be considered. The lower recurrence rate may be partly due to a bias in the type of patient who first presented versus those who were followed up. There are many examples of patients who ignore or are unaware of a visual problem in one eye seeking ophthalmic help only when the second eye is involved. Also, not all the patients were seen by an ophthalmologist in the final review period (1994) during which the data were collected. Recurrence of RVO has been assumed to be symptomatic and, therefore, did not take into account asymptomatic recurrences which could have occurred in a group of patients who answered the questionnaire and were not clinically examined. Recurrence could also have occurred in the deceased group between the last clinic visit and their death. This, however, is a problem inherent in other large long-term ophthalmic follow-up studies of similar conditions.[27,28] In view of the similar methodology used in other reports on recurrence of RVO, and the fact that our recurrence rate was more than halved, medical treatment of underlying conditions may indeed have contributed to a decrease in the rate of recurrence.

Previous studies have hinted at a relationship between smoking and RVO, and in both the original study group and the follow-up group more than 25% of the patients were smokers.[1,2] Smoking, a known cardiovascular risk factor, was increased in those patients with RVO who died.

The increased prevalence of rubeosis iridis in the deceased group is an interesting finding as this has also been observed in other study populations.[29] The incidence of neovascular glaucoma in CRVO has been variously reported as between 13% and 20%.[25,29] A total of 52 patients (49 of 217 with CRVO; 18.7%) from the study group developed rubeosis iridis, but of these 14 (27%) had died. Previous studies have found that patients who develop neovascular glaucoma tend to be older than those who do not,[29] but this age difference was not observed in an analysis of the deceased when compared with the survivors with RVO in our study. This may indicate that other underlying risk factors may be operative, but these are unknown as established cardiovascular risk factors and systemic vascular disease have not been specifically shown to be associated with rubeosis iridis.[29]

Consideration of the role of antiplatelet therapy is raised by the results. Table 3 shows that there was an almost identical percentage of patients on antiplatelet drugs in the two groups (deceased vs survivors). Previous studies have suggested that increased inflammatory activity may exist in patients with RVO,[8] and that increased blood viscosity and platelet activation is a feature in patients with capillary non-perfusion or neovascularisation.[7,30,31] Increased platelet aggregability has also been implicated in incipient CRVO and the release of specific platelet proteins was enhanced in patients with RVO.[32] A role has therefore been postulated for antiplatelet agents in the prevention of recurrence of RVO and in the prevention of further capillary closure.[32] The role of antiplatelet agents in preventing mortality in this group of patients is not confirmed by this study, in contrast to the evidence regarding the benefits of this approach that has been shown by the report of the Antiplatelet Trialist Collaboration and other projects.[33,34]

Approximately two-thirds of the patients with RVO who died during the follow-up study did so from vascular disease (cerebral or cardiac). Comparison of these figures with the causes of death in the West Midlands' population, showed that the proportion of deaths from cardiovascular disease was very similar in the two groups but there was a significant excess number of deaths from acute myocardial infarction in the RVO population. Thus could be due to variations in the way death from cardiovascular disease is documented on the death certificates and possibly there is some overlap between deaths from acute myocardial infarction and deaths from ischaemic heart disease. However, myocardial infarction as the cause of death implies an acute event according to international criteria and it may be that the RVO population is more prone to acute vascular occlusive events. Hankey *et al*.[18] found in their 4 year follow-up of retinal artery occlusion that a coronary event accounted for more than half (59%) of deaths. The percentage of deaths from cardiovascular causes was less in our study (43%) over a longer follow-up period and was similar to that in the West Midlands population as a whole. These data suggest that the cardiovascular prognosis for patients with retinal artery occlusion is worse than for those with RVO. In light of recent trial evidence,[35–37] it is surprising that hypertension and hyperlipidaemia and treatment thereof did not predict death when comparing the deceased with the survivors. However, the deceased population had more clinically evident ischaemic heart disease compared with the survivors.

It is not clear from this study whether there is any relationship between RVO and stroke, and this may be due to the confounding variable of treatment of risk factors undertaken at initial presentation. Medical treatment should tend to reduce the differences, owing to the expected benefit of reduction of stroke rate shown in the hypertensive treatment trials.[35] Despite the potential treatment effects, the number of deaths from stroke in our study was still proportionally higher than for the West Midlands population as a whole. Our results differ substantially from the results reported by Hankey *et al*.[18] with regard to stroke, as they observed in their follow-up of retinal artery occlusion patients that the number of deaths from stroke was small (3%). This could infer a greater link between RVO and cerebrovascular causes of death than retinal artery occlusion.

It is interesting to compare our follow-up study with that of Rubenstein and Jones[19] done some 17 years ago. The number of deaths from vascular disease in our study was lower than was found in Rubenstein's study (62% vs 79.4%) but still proportionally greater than for the general population (54.3%). These differences could again represent a medical treatment effect of associated medical conditions which was not an aggressive part of the treatment regime used in the 1970s. The number of deaths from malignancy was consistent between the populations studied (16.8% vs 20%). Despite the incomplete follow-up in that study, our data are in broad agreement. The total number of deaths from malignant disease was in fact significantly lower in the RVO group compared with the West Midlands population in this study.

We conclude that our data suggest a relationship between RVO increased cardiovascular risk factors, and also increased mortality from myocardial infarction and stroke despite medical intervention. In addition the data confirm the findings of the earlier small incomplete follow-up study in the 1970s.[19] Encouragingly, the concept that reduction of recurrence of RVO and hence a possible disastrous visual outcome may be ameliorated by aggressive medical treatment of underlying cardiovascular risk factors is supported.

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