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Age-related macular degeneration and mortality from cardiovascular disease or stroke

Running title: Age-related macular degeneration and vascular mortality

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Abstract

Background/aims: Age-related macular degeneration (AMD) and vascular disease share similar risk factors. Recent data suggest AMD may independently predict stroke or coronary heart disease. We prospectively assessed the relationship between AMD and risk of stroke- or cardiovascular-related death in an Australian population.

Methods: Of 3654 baseline participants (1992-4) aged 49+years, 2335 were re-examined after 5-years and 1952 after 10-years. Retinal photographs were graded using the Wisconsin System. History and physical examination provided data on possible risk factors. Deaths and cause of death were confirmed by data linkage with the Australian National Death Index. Risk ratios (RR) were estimated in Cox models.

Results: Among persons aged <75 years at baseline, early AMD predicted a doubling of cardiovascular mortality (RR, 2.32; 95% confidence interval (CI), 1.03-5.19), over the next decade, after controlling for traditional cardiovascular risk factors. Late AMD predicted 5-fold higher cardiovascular mortality (RR, 5.57; CI, 1.35-22.99) and 10-fold higher stroke mortality (RR, 10.21; CI, 2.39-43.60) after adjusting for age and sex only. These associations were not present when persons older than 75 were included.

Conclusion: AMD predicted stroke and cardiovascular events over the long-term in persons aged 49-75 years. This may have potential implications for new intravitreal anti-VEGF AMD therapies.

Key Words

Mortality, cardiovascular disease, stroke, age-related macular degeneration, Blue Mountains Eye Study

Introduction

Age-related macular degeneration (AMD), stroke and cardiovascular disease are suggested to share some common cardiovascular risk factors and possibly a common pathogenesis.^{1,2} The potential link between AMD and vascular disease was recently highlighted in data from two large US Studies. The Atherosclerosis Risk in Communities (ARIC) study found that persons with signs of late AMD were significantly more likely than those without AMD to have incident coronary heart disease over 10 years (30.9% versus 10.0%),³ and higher incidence of stroke (4.1% versus 2.1%).⁴ A US Medicare Study found that AMD was associated with 20% higher risk of incident myocardial infarction over 2 years.⁵ AMD has also been linked to decreased survival,⁶ which may reflect underlying non-ocular diseases, such as cardiovascular disease, in persons with AMD.^{3,6} A potential link between AMD and vascular disease would have important therapeutic implications given current concern that some intravitreal anti-vascular endothelial growth factor (VEGF) treatments for AMD could increase stroke risk.^{7,8} We therefore aimed to prospectively assess the link between AMD and cardiovascular- or stroke- related mortality in the Blue Mountains Eye Study (BMES).

Methods

The BMES is a population-based cohort study of common eye diseases in an Australian population, initially aged 49+ years, as described elsewhere.⁹ Of 3654 baseline (1992-4) participants (82.4% participation), 2335 (75.1% of survivors) and 1952 participants (76.6% of survivors) returned to 5- and 10-year examinations respectively. Institutional ethics committee approval and written consent were obtained.

Stereoscopic retinal photographs of both eyes were taken at each examination. Photographic grading for AMD lesions used the Wisconsin System.¹⁰ Assessments of inter- and intra-grader reliability showed good agreement for identifying AMD lesions.⁹ Late AMD was defined as typical neovascular and atrophic AMD lesions.¹⁰ In the absence of late AMD signs, early AMD was defined as large indistinct soft drusen at the macula, or a combination of large distinct soft drusen and retinal pigmentary abnormalities.¹⁰ Questionnaires ascertained medical and social history and fasting blood samples were taken. Hypertension was defined as use of anti-hypertensive medications or a systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 100 mmHg at baseline (Grade 2).¹¹ Diabetes was diagnosed either from medical history or a fasting blood glucose ≥ 7.0 mmol/L.

Demographic data were used to cross-match participants with the Australian National Death Index (NDI) database to confirm deaths over an average 11-year follow-up, using probabilistic record linkage.¹² The sensitivity and specificity of Australian NDI data has been estimated as 93.7% and 100%, respectively, for all deaths, and 92.5% and 89.6%, respectively, for cardiovascular deaths.¹² Validation for stroke deaths is not available. Causes of death were documented from death certificates, and defined using International Classification of Diseases Code (ICD) versions 9, 10. Participants for whom stroke (ICD-9: 430.0-438.9, and ICD-10: I60.0-I69.9) or coronary heart disease (ICD-9: 410.0-9, 411.0-8, 412, 414.0-9, and ICD-10: I21.0-9, I22.0-9, I23.0-8, I24.0-9, I25.0-9) was mentioned in any cause of death, were classified as having a stroke- or cardiovascular-related death respectively.

Statistical Analysis System (SAS Institute, Cary, NC) was used for all analyses. Cox models estimated relative risk (RR) and 95% confidence intervals (CI). Survival time was calculated in days from baseline examination to the date of death or census cut-point of 31 December, 2003. We further stratified the population into two age groups, <75 years and ≥ 75 years, to assess the risk of premature mortality. The <75 year age group also reflects the age range of the recently examined ARIC cohort.³ Final multivariable analyses were adjusted for age,

gender, hypertension, diabetes, smoking and body mass index. We further adjusted for serum lipids, fibrinogen and white cell count. However, these analyses were based on a reduced number of participants because 314 participants at baseline had missing blood data. Additionally, analyses that involved late AMD in participants aged <75 years were only adjusted for age and gender because of the small number of late AMD cases in this subgroup.

Results

We excluded participants with baseline self-reported history of angina, myocardial infarction or stroke (n=713), and those without photographs for AMD assessment (n=100), or with missing data on mortality or cause of death (n=21). Of the remaining 2853 participants included, 51 had late and 130 had early AMD at baseline. Over 11 years, there were 183 cardiovascular-related deaths, 99 stroke-related deaths, and 17 participants were categorised as having died from both stroke- and cardiovascular-related causes.

Table 1 shows the baseline characteristics associated with the presence of AMD signs at baseline and with subsequent stroke- or cardiovascular-related death during follow-up. In general, persons with AMD at baseline were more likely to be older, female, have lower BMI and triglyceride levels, and higher fibrinogen levels. Those who died from cardiovascular or stroke-related death during follow-up were more likely to be older and hypertensive.

Table 1. Baseline characteristics by age-related macular degeneration status at baseline and subsequent cardiovascular- or stroke-related death during follow-up

Baseline characteristic	Age-related macular degeneration			Cardiovascular-related death		Stroke-related death	
	None (n=2672)	Early (n=130)	Late (n=51)	No (n=2670)	Yes (n=183)	No (n=2754)	Yes (n=99)
mean age in years (standard deviation)	64.3 (9.2)	73.7 (8.1)*	81.4 (7.8)*	64.4 (9.2)	75.2 (8.9)*	64.7 (9.4)	76.1 (8.2)*
male sex	41.5	43.1	25.5*	40.7	50.3*	41.3	41.4
diabetes	6.1	8.5	11.8	6.3	7.1	6.3	8.1
hypertension	41.7	41.1	52.0	40.8	57.5*	41.5	52.5*
mean body mass index	26.2	25.8	24.7*	26.1	25.7	26.2	24.6*
mean fasting blood results							
high density lipoprotein cholesterol (mmol/L)	1.5	1.6*	1.6	1.5	1.5	1.5	1.5
total cholesterol (mmol/L)	6.0	6.0	6.1	6.0	6.0	6.0	6.0
triglycerides (mmol/L)	1.7	1.5*	1.7	1.7	1.7	1.7	1.6
white cell count (10 ⁹ cells/L)	6.4	6.6	6.7	6.4	6.5	6.4	6.8
fibrinogen (g/L)	4.0	4.2	4.9*	4.0	4.3*	4.0	4.2
glucose (mmol/L)	5.2	5.0	5.5	5.2	5.3	5.2	5.4
smoking status							
past	34.1	38.5	27.5	34.5	30.2	34.2	35.4
current	14.8	16.9	19.6	14.8	17.6	15.0	13.1

*p<0.05, comparing difference in means or proportions, chi-square test used for discrete risk factors; *t* test used for continuous risk factors (Satterthwaite for unequal variances, otherwise pooled *t* test)

Table 2 shows the association between baseline AMD lesions and cardiovascular-related mortality over the 11-year follow-up. There was no statistically significant association between late or early AMD and subsequent cardiovascular-related death for all ages combined. However, among participants aged <75 years, baseline late and early AMD predicted cardiovascular mortality (**Table 2**). Similarly, among those aged <75 years, baseline late AMD predicted stroke mortality (**Table 3**); although this was based on relatively small numbers. No significant association was found between early AMD and stroke mortality in participants aged <75 years. The association between early AMD and cardiovascular mortality among those aged <75 years became non-significant after further adjusting for serum lipids, fibrinogen and white cell count (data not shown).

Table 2: Longitudinal relationships in the Blue Mountains Eye Study between age-related macular degeneration (AMD) and cardiovascular-related death, stratified by age, after excluding those with a baseline history of stroke, angina or myocardial infarction.

AMD stage	Age Group AMD (late or early)	No. at risk	% affected	Age-gender- adjusted RR (95% CI)*	Multivariable RR (95% CI)†
Late					
Absent	All ages	2802	6.0	1.00	1.00
Present		51	27.4	1.74 (0.97-3.11)	1.56 (0.83-2.95)
Absent	<75 years	2338	3.0	1.00	
Present		9	22.2	5.57 (1.35-22.99)	-
Absent	≥75 years	464	21.1	1.00	1.00
Present		42	28.6	1.43 (0.76-2.67)	1.29 (0.64-2.62)
Early					
Absent	All ages	2723	6.1	1.00	1.00
Present		130	12.3	0.93 (0.55-1.56)	0.95 (0.55-1.63)
Absent	<75 years	2278	2.9	1.00	1.00
Present		69	10.1	2.26 (1.02-4.98)	2.32 (1.03-5.19)
Absent	≥75 years	445	22.7	1.00	1.00
Present		61	14.7	0.61 (0.31-1.21)	0.58 (0.28-1.20)

*Relative risk (95% confidence interval)

†Multivariable relative risk (95% confidence interval) adjusted for age, gender, hypertension, diabetes, cigarette smoking and body mass index. There were too few late AMD cases for further multivariable analysis for participants aged <75 years.

Table 3: Longitudinal relationships in the Blue Mountains Eye Study between age-related macular degeneration (AMD) and stroke-related death, stratified by age, after excluding those with a baseline history of stroke, angina or myocardial infarction.

AMD stage	Age Group AMD (late or early)	No. at risk	% affected	Age-gender- adjusted RR (95% CI)*	Multivariable RR (95% CI)†
Late					
Absent	All ages	2802	3.4	1.00	1.00
Present		51	7.8	0.56 (0.17-1.82)	-
Absent	<75 years	2338	1.4	1.00	
Present		9	22.2	10.21 (2.39-43.60)	-
Absent	≥75 years	464	13.4	1.00	1.00
Present		42	4.8	0.35 (0.08-1.45)	-
Early					
Absent	All ages	2723	3.4	1.00	1.00
Present		130	4.6	0.59 (0.26-1.35)	0.58 (0.25-1.33)
Absent	<75 years	2278	1.5	1.00	1.00
Present		69	0.0	-	-
Absent	≥75 years	445	13.0	1.00	1.00
Present		61	9.8	0.69 (0.30-1.61)	0.67 (0.28-1.56)

*Relative risk (95% confidence interval)

†Multivariable relative risk (95% confidence interval) adjusted for age, gender, hypertension, diabetes, cigarette smoking and body mass index. There were too few late AMD cases for further multivariable.

Discussion

In this study, among participants aged <75 years at their baseline examinations, we found that early AMD predicted higher cardiovascular mortality over the succeeding 11 years. Baseline late AMD was also associated with a higher cardiovascular- or stroke-related mortality risk in this age group, based on a relatively small number of cases. These associations were not found for all ages combined or for persons aged >75 years. In the older group, however, it is likely that other age-related conditions will dominate the mortality risk.

Our findings lend support to ARIC study findings³ which examined the association between AMD and incident coronary heart disease in participants aged 49-73 years. With 80% power and at a 0.05 significance level, our study was powered to detect a minimum RR of 1.7 for the association between early AMD and stroke-related mortality among those aged <75 years. However, because there was no single case of stroke-related mortality among subjects with early AMD in the <75 year age group, we could not confirm the association between early AMD and incident stroke events reported from the ARIC study (hazard ratio, 1.87; CI, 1.21-2.88).⁴ A study of elderly American Medicare enrollees⁵ also recently reported an association between baseline AMD and incident myocardial infarction. However, these data were not adjusted for important confounders such as smoking. Previous studies that examined the cross-sectional association of AMD and cardiovascular disease or stroke also provided inconsistent findings.¹³⁻¹⁵ A few studies have prospectively examined associations between history of stroke or cardiovascular disease and incident AMD, again with inconsistent findings.¹⁶ In our cohort, baseline self-reported history of stroke, angina or myocardial infarction, predicted incident early AMD.¹⁷

With the increasing availability of anti-VEGF therapy, which some reports suggest may increase cardiovascular risk, our results suggest that individuals with a high cardiovascular risk profile may potentially need to be monitored closely if receiving anti-VEGF therapy. Nonetheless, more studies confirming that a link exists between AMD and cardiovascular events would be needed before such recommendations can be made.

Mechanisms for a link between AMD and vascular mortality remain unclear. This association could indicate that AMD is a marker of biological ageing.¹⁸ Alternately, this finding could support the hypothesis that AMD and vascular disease share common antecedents.² Atherosclerosis, inflammation and oxidative stress, implicated in the pathogenesis of both AMD and vascular disease,^{2,4} may be potential mechanisms linking these two diseases. Systemic inflammation has also been identified as a risk factor for both AMD¹⁹ and cardiovascular mortality.²⁰ Variants in the complement factor H gene have recently been identified to predict AMD risk,²¹ and complement activation may also increase risk of stroke.²²

Strengths of our study include its prospective observations from a population-based sample with reasonable follow-up and the use of current gold standard methods to assess AMD. However, our finding that late AMD predicts stroke or cardiovascular mortality was based on relatively small numbers and should be interpreted cautiously. Due to the small number of outcomes, we were unable to adjust for important cardiovascular risk factors such as serum cholesterol levels for the mortality associations with late AMD. We did find that the association between early AMD and cardiovascular mortality became non-significant after adjusting for serum lipids. This could reflect a reduced study power resulting from reduced numbers due to missing blood lipid data at baseline, or indicate that blood lipid profile at least partially explains the observed association between AMD and cardiovascular mortality.

In summary, our BMES data provide support for a possible link between AMD and subsequent stroke and cardiovascular events. The potential association between AMD and vascular disease, and

mechanisms underlying this relationship, deserve further study. Its confirmation would have important implications, given current concern that anti-VEGF treatments for AMD could increase stroke risk.^{7;8}

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